Immune Brain*

"Immune-Brain": A case series of cognitive dysfunction/decline in cancer patients on immunotherapy

Sarah Gillett, Ximena Jordan-Bruno, Hibba Rehman, Alissa Thomas

The University of Vermont Medical Center

Background: Cognitive dysfunction/decline (CD) is a well-known side effect of conventional chemotherapy (i.e. "chemo-brain"), but the neuro-cognitive impact of checkpoint inhibitor immunotherapy (IO) is not well described, despite the known potential for inflammatory neurotoxicities.

Methods: From January 2015-December 2018 at University of Vermont Medical Center, we retrospectively identified cancer patients who received at least one infusion of IO and had a concurrent diagnosis of CD on the problem list, medical history, or billing codes. We manually reviewed the charts of all patients meeting this criteria and excluded patients with an alternative diagnosis that was causal for CD.

Results: We identified 55 patients and excluded 16 for CD before IO started, 23 with toxic/metabolic causes (including stroke, sepsis, medications, seizures), 4 for primary central nervous system malignancy, and 6 for CD related to new or worsening brain metastases. Six had CD possibly related to IO (table). Most had also received chemotherapy either concurrently or prior to starting IO, but two patients had only ever received IO cancer therapy. Four of the six had documented MMSE or neuropsychological testing. On careful chart review, no alternative diagnosis was identified as clearly causal for the change in cognition.

Conclusions: Patients receiving IO cancer therapy do report CD, which has not been broadly described. Prospective pre- and post-treatment cognitive monitoring may identify more patients with neurocognitive symptoms related to immunotherapy. Future research is needed to report incidence of potential IO-related CD and to develop preventative or therapeutic strategies.

THE University of Vermont CANCER CENTER

IMMUNE BRAIN: A CASE SERIES

UVMHealth.org/CancerCenter

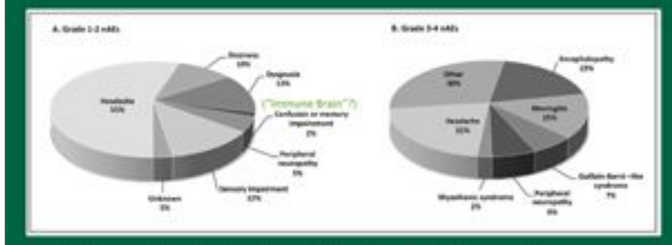
Sarah Gillett, MD, PhD, Ximena Jordan-Bruno, MD, Hibba Rehman, MD, Alissa Thomas, MD

Background

Cognitive complaints reported to be up to 75% in patients receiving conventional cancer therapy ("Chemo Brain")

- difficulty concentrating
- memory impairment
- Fatigue
- increased anxiety and depression
- affects learning, executive function, and processing speed

Studies of checkpoint inhibitors report neurologic adverse events in up to 28% of participants



No formal collection of cognitive data or uniform coding mechanism makes it likely mild or transient neurocognitive complaints and neurologic immunotoxicity are under reported

Study Design

Retrospective Chart Review

January 2015-Decmber 2018 at University of Vermont Medical Center

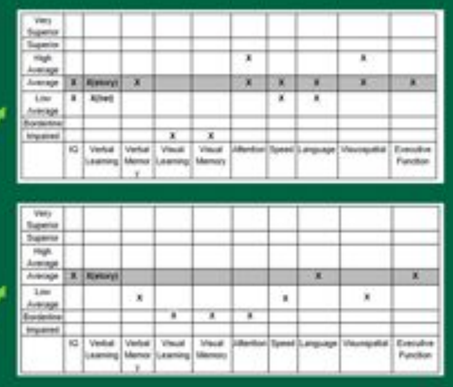
- Cancer patients
- received at least one infusion of checkpoint inhibitor immunotherapy *and*
- had a concurrent cognitive diagnosis
  - problem list, medical history, or billing codes
  - search terms: cognitive impairment, mild cognitive impairment, neurodegenerative cognitive impairment, memory change/memory deficit/memory difficulty/memory impairment, altered mental status, or encephalopathy
- Excluded patients with an alternative diagnosis that was causal for CD (stroke, sepsis, seizure, brain tumor).

PATIENT	IO/ #INFUSIONS	PRIOR CHEMO	CLINICAL COURSE
54 YO M NASO-PHARYNGEAL	Pembrolizumab 47	5-FU, cisplatin	After 43 cycles of IO, reported progressive short-term memory loss, inattention, slowed information processing, speech, language, and executive function changes worsening over 6 months. Confirmed by formal neuropsychological testing
69 YO F NSCLC	Nivolumab 15 Pembrolizumab 18	carboplatin/ Pemetrexed, EC1456, gemcitabine/ vinorelbine	After 14 cycles pembrolizumab (and 1 year after 15 cycles nivolumab) reported memory loss and word finding difficulties worsening over 6 months. Confirmed with formal neuropsychological testing
77 YO M NSCLC	Pembrolizumab 11	Carboplatin/paclitaxel	Patient with dementia had worsening dementia after 6 cycles IO, confirmed on MMSE (15 to 10 to 8)
85 YO M MELANOMA	Nivolumab 9	-	Patient with dementia had worsening dementia after 9 cycles IO, confirmed on MMSE (13 to 11)
67 YO F NSCLC	Pembrolizumab 2	-	Patient had an episode of encephalopathy without identified cause and skin rash following second dose of IO, which was then discontinued
75 YO M NSCLC	Nivolumab 9	Carboplatin/gemcitabine Docetaxel	After 9 cycles of IO (with docetaxel 1st 6 cycles), reported memory loss first attributed to metabolic causes. This was again noticed in throughout 2017 with unclear cause, patient refused formal testing

Formal Neuropsychologic testing

Performed in 2 patients

Interestingly revealed 2 patients who had cognitive deficits or decline in visuospatial memory



Strengths and Limitations

Strengths

- Robust medical record review
- Leveraging of electronically collected medical data

Limitations

- Retrospective, likely incomplete capture and missing many more subtle cases
- Cannot interpret effects of prior chemo

Selected References

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2. Joly, F., et al. Potential Effect of Immunotherapy Agents on Cognitive Function in Cancer Patients. JNCI: Journal of the National Cancer Institute, 2019. 112(2): p. 123-127
3. Perrinjaquet et al. Neurotoxicity associated with cancer immunotherapy. Curr Opin Neurol 32(3). 1350-7540

Take Home Points

This case series provides proof of concept that cancer patients on checkpoint inhibitors do report cognitive impairments, possibly related to immunotherapy toxicity

2 formally tested cases showed impairment in visuospatial memory/learning

Future Directions

Prospective studies are needed to assess the true incidence of "Immune-brain", Identify risk factors and biomarkers, and develop preventive and therapeutic strategies

We are developing a pilot study in lung cancer patients to involve formal neuropsychological testing before and after starting immune therapy at UVMMC

Impact of Proton Pump Inhibitors*

Impact of Proton Pump Inhibitors on the efficacy of Immune Checkpoint Inhibitors in Metastatic Malignant Melanoma

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1 Norris Cotton Cancer Center at Dartmouth-Hitchcock Medical Center, 2 The Dartlab at Dartmouth College

Background: Acidic microenvironment facilitates tumor growth. Mouse models showed proton pump inhibitors (PPI), causing neutralization of the acidic tumor microenvironment and inhibiting tumor growth. PPIs also sensitize the resistant tumors to immunotherapy and modify the gut microbiota, influencing the efficacy of immune checkpoint inhibitors (ICI). Clinical studies have shown the variable impact of PPIs on ICI efficacy, ranging from no benefit to a negative impact.

Methods: We retrospectively analyzed 120 metastatic malignant melanoma patients treated with ipilimumab alone or with nivolumab, and pembrolizumab. Cohort A included patients taking PPI at the time of ICI initiation. Cohort B included non-PPI users. Objective response rate (ORR) and progression free survival (PFS) were the primary outcomes. Cox regression univariate and multivariate analyses were performed. Fisher's exact test was used to compare grade 3 or 4 immune-related adverse events (IrAE).

Results: Cohort A included 29 (24.2%) patients, of which 68.7% were male. The median age was 65 years. The proportion of the patients taking ipilimumab or pembrolizumab was the same (48.3% vs. 44.8%). Significantly higher proportion of patients achieved ORR and DCR in cohort A [76%, OR= 3.8, P= 0.009 and 84%, OR=4.3, P= 0.013]. The median PFS was significantly higher in cohort A [A=27.6 vs. B=4.4 months, HR=0.3, P= 0.005]. Median OS was higher in cohort A without significance [A=39.3 vs. B=28.0 months, HR= 1.01, P= 0.9]. PPI did not significantly increase the Odds of having grade 3 or 4 IrAE.

Conclusions: We observed favorable outcomes in patients receiving PPI when starting ICI, contrary to some of the studies suggesting the negative impact of PPI on ICI efficacy. Prospective studies are needed to evaluate the real effect of PPI on ICI.

Impact of Proton Pump Inhibitors on the efficacy of Immune Checkpoint Inhibitors in Metastatic Malignant Melanoma

Muhammad Zubair Afzal, MD, MS*, Tayyaba Sarwar MBBS, MS, Keisuke Shirai MD, MSc***

Department of Hematology-Oncology, Norris Cotton Cancer Center at Dartmouth-Hitchcock*, The Dartlab at Dartmouth College**

BACKGROUND

Proton pump inhibitors (PPI's) are one of the most commonly used chronic medications. Over the course of past several years, annual prevalence of PPI has increased from 8.5 per 100 persons to 15.5 per 100 persons. Immune checkpoint inhibitors (ICI's) are the frontline treatment in malignant melanoma. Ipilimumab was the first ICI approved by FDA for treatment of malignant melanoma in 2011. Nivolumab and pembrolizumab were approved in 2014 for treatment of unresectable or metastatic malignant melanoma. Since 2014, the 5-year survival has increased from 10% to 22.5% in malignant melanoma. As PPI's are one of the most commonly used chronic medications and the ICI's are also increasingly used not only in malignant melanoma but has also been approved in many other malignancies as well. With that, there is an increase risk of drug-drug interaction (DDI), that can increase or decrease the efficacy of the anti-tumor therapy. In mouse models, PPI alter the tumor microenvironment (TME) and create a neutralizing environment. Acidic TME results in the growth and progression of the tumor. PPI also alter the microbiota of the gut and influence the efficacy of the ICI (Xerograft models). A population-based retrospective study in Iceland failed to show any chemoprotective effect of PPI in patients with breast, prostate cancers and malignant melanoma. Mukerjee et al studied the immune modulating effect of PPI on the efficacy of PD-1 and PD-L1 in 158 patients with different malignancies and no difference in OS and PFS was observed. Homicsko et al conducted this retrospective analysis of data from 140 participants in the Checkmate 069 (NCT019274199) phase II clinical trial. Univariate analysis showed that PPI treatment received by patients that was detected at baseline decreased the objective response rates (ORR) almost by half, and also reduced the length of PFS and OS in patients treated with ipilimumab and nivolumab but not with ipilimumab alone.

Due to these variable results in clinical and pre-clinical studies we performed a retrospective on patients with malignant melanoma on ICI who have been taking PPI concurrently.

MATERIALS AND METHODS

This study was conducted at Norris Cotton Cancer Center. Patients with malignant melanoma were selected from 01/01/2011 until 12/31/2017. Institutional Review Board (IRB) approved the study and granted the exemption from informed consent.

Inclusion Criteria:

Patients ≥ 18 years, diagnosed with malignant melanoma with AJCC Ed.7 clinical stage IIIC (Unresectable) or stage IV (metastatic), who have received at least one does of FDA approved Ipilimumab, Nivolumab, Pembrolizumab or Ipilimumab/Nivolumab combination.

Exclusion Criteria:

Only exclusion was the patients under 18 years of age.

Cohort A included patients on PPI's at the time of ICI initiation (identified through review of medication records in EMR). Cohort B included patients on ICI but not on PPI

We recorded the basic demographics, somatic mutations, metastatic status, prior therapies objective response rate (ORR), disease control rate (DCR), overall survival (OS), and progression free survival (PFS), and immune related adverse events (IrAE).

Cox regression univariate and multivariate analyses were performed for overall and progression free survival. Fisher's exact test was applied for categorical variables. Survival analyses were adjusted for age at diagnosis, sex, metastatic status, mutations, type of ICI's, prior therapy, prior radiation, comorbidities.

Primary Endpoint

The primary endpoint was ORR

Secondary Endpoint

Secondary endpoints were OS, PFS, and DCR

RESULTS

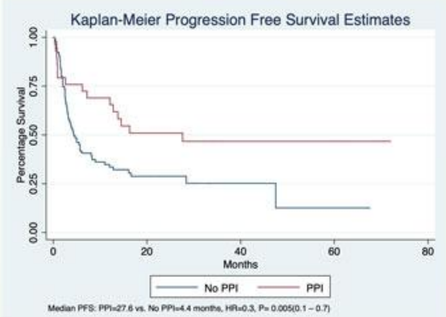
A total of 120 patients were identified. Overall majority of the patients were male (63.3%). Median Age at the time of diagnosis was 64 years Majority of the patients had stage IV disease (94%) Only 5% patients had unresectable stage IIIC.

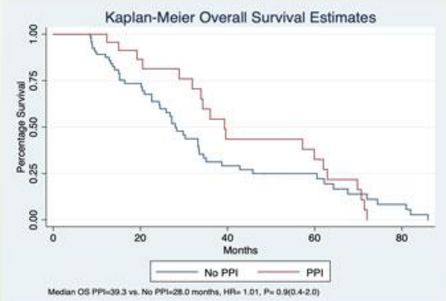
	No PPI (N=91)	PPI (N=29)	P-Value
Sex Male Female	 56 (61.5%) 35 (38.5%)	 20 (68.9%) 9 (31.1%)	 P= 0.5
Median Age (Years)	64	65	
Anti-PD-1 (Pembrolizumab and Nivolumab)	34 (37.4%)	12 (41.4%)	P=0.7
Anti-CTLA4 (Ipilimumab)	38 (41.7%)	14 (48.3%)	P=0.5
Anti-PD-1/Anti-CTLA4 (Ipilimumab/Nivolumab)	16 (17.6%)	2 (6.9%)	P= 0.2
AJCC 7th edition Clinical Stage IIIC IV	 5 (5.5%) 86 (94.5%)	 1 (3.4%) 28 (96.6%)	 P=0.7
Metastatic Status M1a M1b M1c M1d	 12 (13.8%) 20 (22.9%) 33 (37.9%) 22 (25.3%)	 1 (3.6%) 9 (32.1%) 8 (28.6%) 10 (35.7%)	 P=0.2
Liver Metastases	26 (28.6%)	7 (24.1%)	P=0.6
Brain Metastases	20 (21.9%	9 (31%)	P=0.3
Skeletal Metastases	21 (23.1%)	3 (10.3%)	P=0.1
BRAF/MEK Status	33 (36.3%)	9 (31.0%)	P=0.6
Prior Therapy (Chemotherapy/ Interferon/Adjuvant ICI	29 (31.9%)	10 (34.5%)	P=0.7
Prior Radiation Therapy	17 (18.7%)	3 (10.3%)	P=0.2
Current Status Alive Dead	 49 (53.8%) 42 (46.2%)	 19 (65.5%) 10 (34.5%)	 P=0.2
Progression	65 (71.4%)	15 (51.7%)	P=0.07
IrAE's	52 (57.1%)	12 (41.4%)	P=0.1
ECOG-PS 0 1 2 3	 45 (49.5%) 35 (38.5%) 7 (7.7%) 3 (3.3%)	 13 (44.8%) 11 (37.9%) 3 (10.3%) 0 (0%)	 P=0.7

Ipilimumab (14= 48.3%) Ipilimumab+Nivolumab (2 (6.9%) Pembrolizumab or Nivolumab (13= 44.8%)	Pantoprazole (8= 27.6%) Omeprazole (17 = 58.6%) Esomeprazole (2= 6.9%) Lansoprazole (2= 6.9%)

Variables	ORR	OR (95%CI)/P-Value	DCR	OR (95%)/P-value
PPI Yes (N= 25) No (N= 84)	76%	3.8 (1.39 – 10.5)/ 0.009	84%	4.3 (1.37 – 13.7)/ 0.013

RESULTS





DISCUSSION AND CONCLUSION

Although, mouse models, and xenografts have shown beneficial effect of PPI on the tumor regression and amplifying the effect of ICI. However, the clinical data (mainly retrospective) contradicts the results of pre-clinical studies. Our study, although retrospective, supports the results of pre-clinical models. This is a well matched study population. Contrary to other studies, there are significant differences in the primary and secondary endpoints except overall survival. Since PPI's are one of the most commonly used chronic medications , we need prospective studies to evaluate its effect on ICI.

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Literature Review of Prehabilitation

Literature Review of Implementation and Benefits of Prehabilitation for Gastrointestinal Cancers

Gagne S, Ho T, Dumond K, Yaitanes D, Joseph A, Boegemann J, Litterini A

University of New England

Background: Cancer treatment can cause physical deficits across the continuum of care. Prehabilitation, the stage between diagnosis and acute intervention, may be considered a feasible and effective means of mitigating negative health outcomes (e.g. prolonged perioperative length of stay [LOS], decreased functional capacity [FC] and reduced lean body mass [LBM]) post-operatively for gastrointestinal cancer.

Methods: A literature review was conducted by University of New England doctor of physical therapy students using the following inclusion criteria: written in English; adults (age 18-90); published since 2013; and randomized controlled trials. Search terms were: “prehab”; “prehabilitation”; “pre-surgery”; “colorectal cancer”; “gastrointestinal cancer”; “pancreatic cancer”; “esophageal cancer”; and “abdominal cancer”. No results were identified in PubMed, CINAHL, or Cochrane Library. The inclusion criteria were modified to include “clinical trials”, and resulted in 59 articles.

Results: Twenty-one articles were included in the final review (colorectal [CRC]: 12, pancreatic: 6, other GI: 4). Prehabilitation (supervised and unsupervised) was beneficial for gastrointestinal cancer survivors undergoing surgery. Body weight and LBM following prehabilitation had a slower deterioration effect post-surgery. CRC survivors participating in prehabilitation had decreased LOS, decreased loss of FC, and decreased loss of LBM. Pancreatic cancer survivors participating in supervised full body strengthening and aerobic exercise pre-surgery had decreased pulmonary complications.

Conclusions: These findings suggest gastrointestinal cancer survivors participating in both supervised or unsupervised prehabilitation may decrease their perioperative LOS. Improvements in FC, and maintenance of LBM, decrease the risk of post-surgical complications. Further research regarding prehabilitation in gastrointestinal cancer survivors is needed due to limited available literature.

Literature Review of Prehabilitation Interventions and Outcomes for Gastrointestinal Cancers

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Introduction

- *Prehabilitation* (prehab) is the stage of cancer rehabilitation between diagnosis and acute intervention that utilizes targeted physical activity to "reduce severity of current and future impairments".[1]
- The purpose of this literature review was to develop a theoretical framework for future research and guidance for implementation of effective prehab for gastrointestinal cancer survivors undergoing surgical treatment in Maine.

Methods

- A literature review of 59 scholarly studies was conducted to analyze the type of exercise applied during prehabilitation programs as well as postoperative outcomes for gastrointestinal (GI) tumor resection.
- Studies published in English between 2013-2019 were included (21).
- Due to lack of available systematic reviews and randomized controlled trials, inclusion criteria was widened to include controlled clinical trials.

Colorectal Cancer

Unsupervised, Home-Based Intervention

- Meaningful changes in postoperative functional exercise capacity can be achieved with a home-based program.[2]
- Participation had positive effects on physical activity levels and functional walking capacity within the 4-week preoperative period.[3]

Supervised and Unsupervised Intervention

- Four weeks of unsupervised prehabilitation is sufficient to modify exercise behavior.[3]
- OncoActive intervention provides opportunity to accelerate cancer recovery.[4]
- Participation in prehab reduces the chances of losing lean body mass.[5]
- Nutritional prehab can decrease length of hospital stay whether alone or paired with exercise.[6]
- Sedentary patients will benefit from prehab.[7]
- A prehab program instituted within the 4-5 week period between diagnosis and surgery is feasible for achieving clinically relevant effects in post-surgical recovery.[8]
- In frail patients undergoing colorectal cancer resection, a multimodal prehab program did not affect postoperative outcomes.[9]
- Trimodal prehab is associated with improved 5-year disease free survival in all stages of colorectal cancer.[10]
- Endurance and resistance training results in improvements in functional capacity based on 6-Minute Walk Distance.[11]
- A cardiopulmorary-based prehab program does not significantly reduce postoperative complications or length of hospital stay.[12]

Pancreatic Cancer

Unsupervised, Home-Based Intervention

- Increase in physical fitness reduces postoperative complications, hospital stay, and associated costs.[13,14,15]
- Home-based intervention may improve patient adherence rates to exercise.[16,17]
- There are no significant differences between exercise adherence rates and phase of neoadjuvant therapy.[18]
- American College of Sports Medicine (ACSM) guidelines[19] for aerobic exercise present a reasonable target for patients with pancreatic cancer undergoing neoadjuvant therapies.[18]
- Aerobic exercise and full body strength training decrease postoperative pulmonary complications.[15]

Supervised Intervention

- Increases in muscle strength and body weight are more significant following supervised progressive resistance training.[17]

Other Gastrointestinal Cancers

Unsupervised, Home-Based Intervention

- Aerobic exercise and strength training may mitigate surgery-related decline associated with malignant gastroesophageal lesions.[20]

Supervised and Unsupervised Intervention

- Prehab may decrease requirement of vasoactive drugs during surgery, rate of surgical complications, cardiovascular complications, risk of infection, paralytic ileus, as well as intensive care unit length of stay.[21]
- Exercise programs consisting of 15-60 minutes per session, 2-3 times per week, and aerobic and strength training movements, can cause improvements in cardiopulmonary fitness and functional capacity, and can be used for future goals in prehab programs.[22]

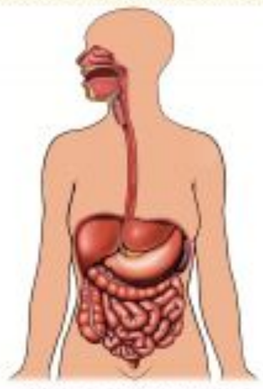
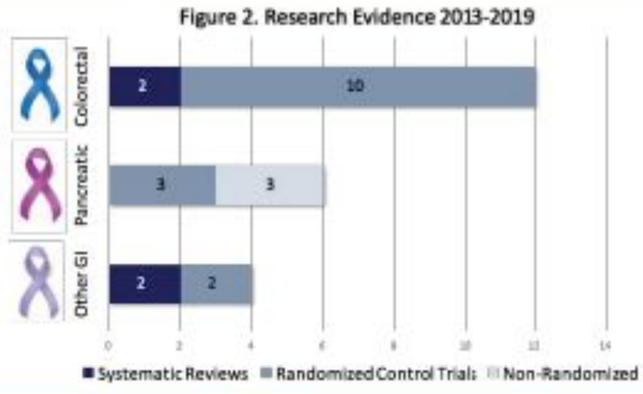


Figure. 1 Gastrointestinal Tract



Conclusions

- Participation in a multi-modal prehab program is feasible for GI cancer survivors undergoing surgical intervention.
- It is important to note that many of the studies on unsupervised exercise initiated the program with a supervised introductory session.
- Future research should focus on multimodal, supervised prehab with objective monitoring of progress.[23]
- ACSM guidelines recommend the use of supervised physical activity for best outcomes following prehabilitation.[19]

Acknowledgements

The authors would like to thank Dr. Timothy Fitzgerald of Maine Medical Center Cancer Institute for conceptualization of this literature review and the the University of New England librarians for search assistance.

References

Maximizing Oncology Patient Throughput

Maximizing Oncology Patient Throughput While Maintaining Social Distancing Guidelines for COVID19

Joshua Hickman, Jennifer Snide, Stephanie Davis, Cristan Howard

D-HH - Norris Cotton Cancer Center

Background: This method of data analysis was adopted and used to test the impact of clinic volumes and flow of oncology patients to our clinic at Norris Cotton Cancer Center (NCCC) Lebanon during COVID-19. With no published methods on how to decrease clinic volumes due to pandemic, we were left with using existing capacity management tools to maintain safe patient throughput of an average of 200 appointments per day in accordance to organizational social distancing guidelines.

Methods: Members of the NCCC leadership team used existing data and analytical tools, which were previously deployed for pre-COVID initiatives, to assess volume impact to a clinical system that was trying to establish new standards for social distancing. Sources of data abstraction were started in Dartmouth-Hitchcock programs which were exported to Microsoft Excel for review and manipulation.

Data was used to assess daily and weekly capacities to establish clinic capacities and better manage patient throughput. Graphs and charts were used with Plan-Do-Study-Act (PDSA) formats to make changes to processes that pre-determined how we schedule and see patients within our clinic.

Results: Through the data analysis, we were able to establish and monitor hourly capacities in our clinics to maintain adequate social distancing during COVID-19. Capacities we examined were number of spaces within our waiting rooms and number of exam rooms available (n=25). These tools were designed to be scalable which were used to change capacities due to resources being variable by day of the week. Through PDSA methods, we established hourly and daily capacities of patients based upon the number of patients we could move through our clinics per hour.

As a result of using existing data analysis tools, we were able to conceptualize new tools to help us during a time where we needed to increase our clinic volumes to meet demand.

Conclusions: With proper data metrics, we successfully were able to establish clinical capacities for all in person appointments at our Lebanon NCCC clinic. By further understanding our maximum patient throughput per hour, we were further able to establish goals and usage of technology based options for clinic visits such as telephone calls or video tele-medicine. The need for these technology based options ranged from 6% to 17% per day to maintain organizational social distancing practices.

The methods of using existing tools and new tools led to a movement to use them in an organizational wide format which gave all clinics access to the tools developed within the NCCC. These tools were used to help clinic management teams assess hourly, daily and weekly volumes to better plan schedules and resources needed to care for patients during the COVID-19 pandemic.

An Interprofessional Hospice Training Pilot Program for Allied Health Care Major Students

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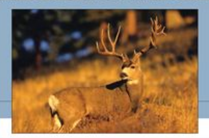
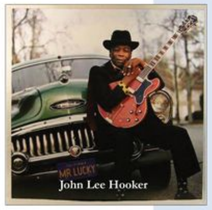
[1]Doctor of Physical Therapy Program, University of New England, Portland, ME; [2]Compassus Hospice, Scarborough, ME

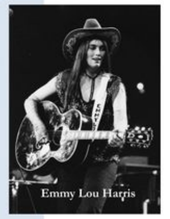
Background: Hospice and palliative care training and exposure are critical components within the curricula of allied health care education majors. Developing opportunities for students through community collaborations is necessary to address this need.

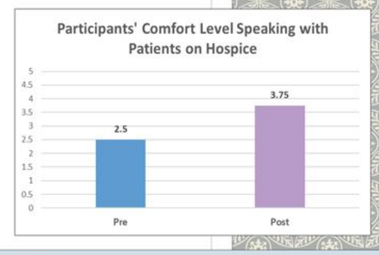
The purpose of this pilot initiative was to assess the feasibility of a formal program collaboration between an academic institution and a local hospice provider.



Results: Six student-mentor pairs worked with six patients receiving hospice for companionship and the creation and presentation of a Life Book. All pairs successfully completed the program and Life Books were presented to the patients at a final visit celebration. Four students completed both pre- and post-survey data. Comfort level working with patients on hospice increased following participation in the pilot program (2.5 to 3.75 on scale of 1 to 5).







Methods: The University of New England partnered with Compassus Hospice for the "Celebrate Life" pilot program in spring, 2019. Evening trainings, with dinner provided, accommodated the students' course schedules.

Six healthcare major students (physical therapy, occupational therapy and social work) completed formal hospice volunteer training and were matched with an experienced volunteer or faculty mentor to provide 6-8 companionship visits with a patient enrolled in hospice to develop a Life Book. Pre- and post-surveys were completed electronically to assess attitudes, motivations and comfort level for working with patients receiving hospice.

A 67 y.o. single male patient on hospice for advanced heart disease participated in the Celebrate Life Program. Raised in New York, he moved to the coast of Maine in his thirties. He was a mason and a clam digger, loved hunting, music and the Yankees. He died one month after participating.

Conclusion:

This project demonstrated the feasibility of a pilot program collaboration with positive outcomes observed for the participants. Experiential opportunities with virtual reality scenarios and observations in other hospice settings are being explored and utilized to further enhance the hospice training experience for students.

Acknowledgements: We would like to express appreciation to RS for sharing his life story and to Compassus Hospice for this rich learning opportunity.

Patient Reported Outcomes: Cellular Therapy

Patient Reported Outcomes in Patients Undergoing Cellular Therapy at Dartmouth Hitchcock

Alexandra Donovan, A. Hali Roy, Dorothy McKenna, Charlotte Coughenour, Kate Caldon, Lisa Wesinger, Lynn Root, Christi Hayes, Kenneth Meehan, MD

DHMC - Norris Cotton Cancer Center

Background: Patient reported outcomes (PROs) are a measure of any aspect of a patient's health that comes directly from the patient, without interpretation by a clinician. Several PRO studies have demonstrated increased fatigue, depression, anxiety post-hematopoietic stem cell transplant. Other studies have demonstrated correlation between PROs and objective outcomes such as overall survival and GVHD. Here we evaluate PROs in patients undergoing cellular therapy at Dartmouth-Hitchcock as a needs assessment to determine how to improve such PROs.

Methods: Patients undergoing hematopoietic stem cell transplant or CAR-T cell therapy at DHMC were provided with two surveys, the PROMIS-29 and NCCN Distress Thermometer, which were collected at baseline (pre-cellular therapy), and 1mo, 3mo, 6mo, and 12mo post-cellular therapy. PRO scores were interpreted using the NIH PROMIS tools, and compared between and among patients.

Results: A total of 32 patients had enrolled at time of this interim evaluation, with analysis conducted on 18 patients completing surveys at more than one time point. Surprisingly, our surveys reveal most patients report decreased anxiety at 1mo post-transplant compared to baseline; however, most patients report worse depression and fatigue 1mo post-transplant. Most patients demonstrated worse outcomes 1mo post transplant with improved symptoms at 3-6mo post-transplant.

Conclusions: Our interim analysis demonstrates increased depression and fatigue post transplant, with reduced anxiety post-transplant. These symptoms were most heavily reported at 1-3 months, and suggest interval improvement in symptoms starting at 6 months post-transplant.

Notes: Future Directions: Despite many studies evaluating, few studies have addressed interventions designed to improve PROs. We are currently developing a study evaluating the effects of a psychosocial educational intervention on PROs with hopes of reducing anxiety, depression, and fatigue post-cellular therapy.

Patient Reported Outcomes in Patients Undergoing Cellular Therapy

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Background

- Patient reported outcomes (PROs) are measures of a patient's health that come directly from the patient, without interpretation from a physician.
- Several studies have demonstrated correlation between PROs and objective outcomes in the hematopoietic stem cell transplant (HSCT) population.
- However, few studies have evaluated interventions aimed to improve PROs.
- We evaluate PROs in patients undergoing cellular therapy at Dartmouth-Hitchcock (DHMC) as a needs-assessment to determine how to improve PROs.

Methods

- Patients undergoing HSCT or CAR-T cell therapy at DHMC were provided with the PROMIS-29 survey (NIH standardized PROs collection tool) and NCCN Distress Thermometer and Problem List.
- Surveys were collected pre-cellular therapy, and at 1, 3, 6, and 12 months post-cellular therapy.
- PRO scores were calculated using the NIH HealthMeasures.net tool.

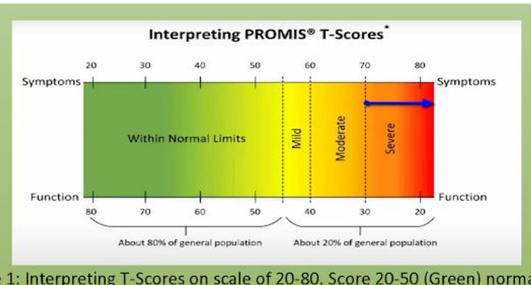

Figure 1: Interpreting T-Scores on scale of 20-80. Score 20-50 (Green) normal. Increasing score associated with negative outcome, decrease in score suggests improvement

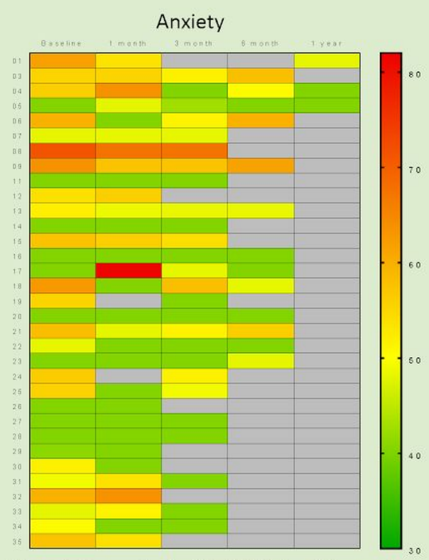

Figure 2: T-scores for Anxiety. 13/33 pts w/ decreased anxiety from baseline (BL) to 1 mo, 7/33 w/ increased anxiety BL to 1 mo. 6/13 pts report increased anxiety from 3 mos to 6 mos.

Figure 3: T-scores for Depression. 5/33 pts w/ decreased depression from baseline (BL) to 1 mo, 10/33 w/ increased depression BL to 1 mo. General reduction in depression by 6 mos.

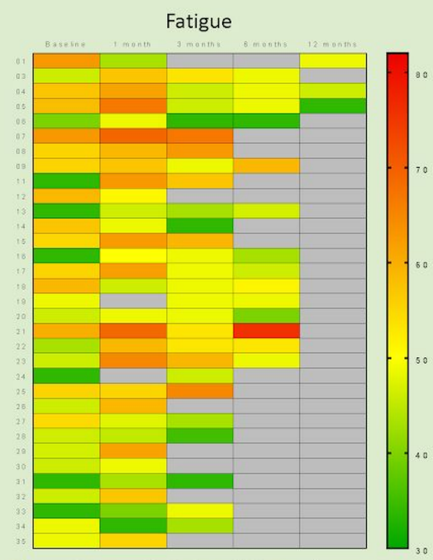

Figure 4: T-scores for Fatigue. 6/23 pts w/ decreased fatigue from baseline (BL) to 1 mo, 23/33 w/ increased fatigue BL to 1 mo. Persistent fatigue reported at 6 mos.

Results

- At the time of our interim evaluation, 46 patients had been accrued.
- Analysis was performed on 33 patients completing at least 2 surveys post-transplant.
- Our data reveal that most patients report decreased anxiety at 1 mo post-transplant compared to baseline, though half of those reaching 6 mos report increased anxiety at 6 mos.
- Most patients report worse depression and fatigue 1 mo post-transplant.
- Early data suggests reduced depression and fatigue starting at 3-6 mos post-transplant compared to baseline, though most patients still endorse higher levels of anxiety and fatigue compared to the general population.

Conclusions

- Our analysis demonstrates increased depression and fatigue post-transplant, with reduced anxiety immediately post-transplant.
- These symptoms were most heavily reported at 1-3 mos post-therapy and do not recover to that of the normal population, offering an ideal time to address symptoms with an intervention.

Future Directions

- Plan to stratify differences in outcomes between disease process and type of therapy (ex: auto vs. allo or HSCT vs. CAR-T).
- Few studies have addressed interventions to improve PROs in this population. We are developing a psychosocial educational intervention aimed to reduce anxiety, depression, and fatigue post-cellular therapy.

Potential Germline Findings: Somatic Tumor Testing

Potential germline findings identified during somatic tumor testing: room for improvement.

Heather Wright[1], Sundas Khan[2], Melissa Cuke[2], Marie Wood[2]

1 DHMC, 2 UVM

Background: Genomic testing, useful for treatment planning and identification of patients for clinical trials, may indicate the presence of a germline mutation. We sought to evaluate the incidence of potentially actionable germline mutations detected via genomic testing and determined rates of germline testing among patients with potential germline mutations.

Methods: We conducted a retrospective review at the University of Vermont between 03/02-11/19 of patients undergoing genomic testing that was reviewed for mutations in 60 genes associated with hereditary cancer. Proportions with 95% confidence intervals are presented and comparisons made using a X2 test.

Results: 342 patients underwent genomic testing over the study period. 59% (203/342) had a mutation in ≥ 1 gene associated with hereditary cancer. Most common tumor types with potential germline mutations include: NSCLCA (25%), CNS (18%), ovarian (8%) and sarcoma (8%). Potential germline mutations were most commonly identified in TP53, CDKN2A, PTEN, and RB1. 58 patients underwent germline testing of which 19% were positive for germline mutations. Of patients with mutations in the highly penetrant BRCA, PALB2, and Lynch genes, 71% were positive for germline mutations. Only 18% (36/203) of patients with potential germline results were referred for genetic counseling.

Conclusions: Genomic testing can reveal hereditary cancer syndromes. 19% of patients who underwent genetic testing in this cohort had a pathogenic germline mutation which enriched to 71% when considering genes rarely mutated in tumors (BRCA, PALB2, and Lynch genes). Only 17% of this cohort underwent genetic testing, representing a significant missed opportunity given the implications of these findings for both patients and families.

POTENTIAL GERMLINE FINDINGS IDENTIFIED DURING SOMATIC TUMOR TESTING: ROOM FOR IMPROVEMENT

S. Khan[1], H. Wright[2], M. Cuke[1], M. Wood[1]

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Introduction

- Hereditary cancer syndromes account for about 5-10% of cancers
- Hereditary cancers are typically identified through a process of genetic counseling and testing
- Genomic testing (performed on tumor tissues) can reveal potential germline mutations. However, the germline status needs to be confirmed through germline testing

Aims

1. **To determine the incidence of germline mutations detected via genomic testing**
2. **To identify the rates of germline testing for patients with potential germline findings on genomic testing**

Methods

Study population

Cancer diagnosis + genomic testing through FoundationOne at the University of Vermont Medical Center

N=342 cases

Review of genomic test reports

- Incidental findings: somatic mutations in actionable genes[1]

Cases with potentially actionable mutations

Review of electronic medical charts

- Follow-up germline testing

Results

Figure 1. Genomic and Germline results in study population

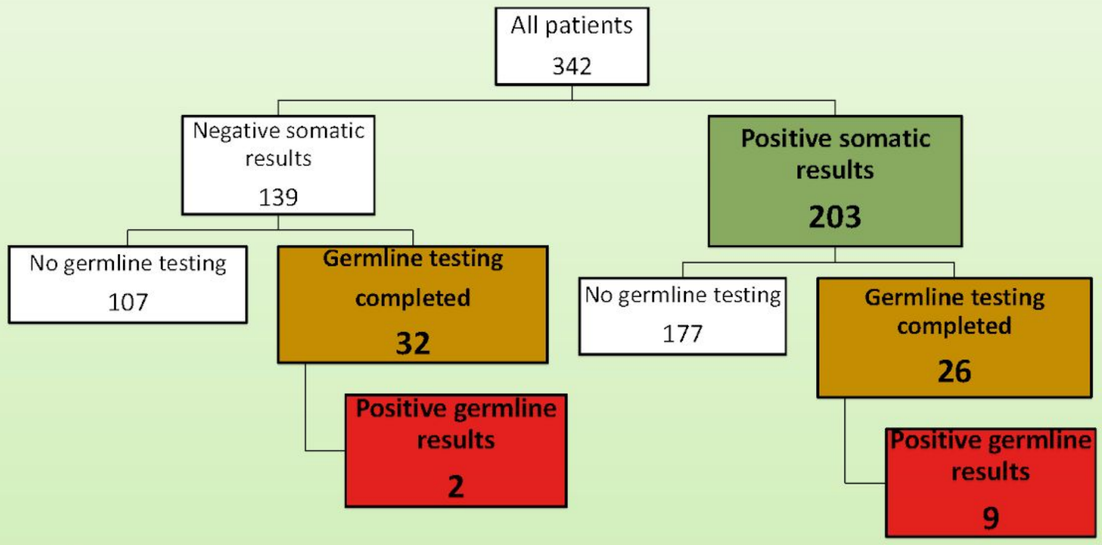
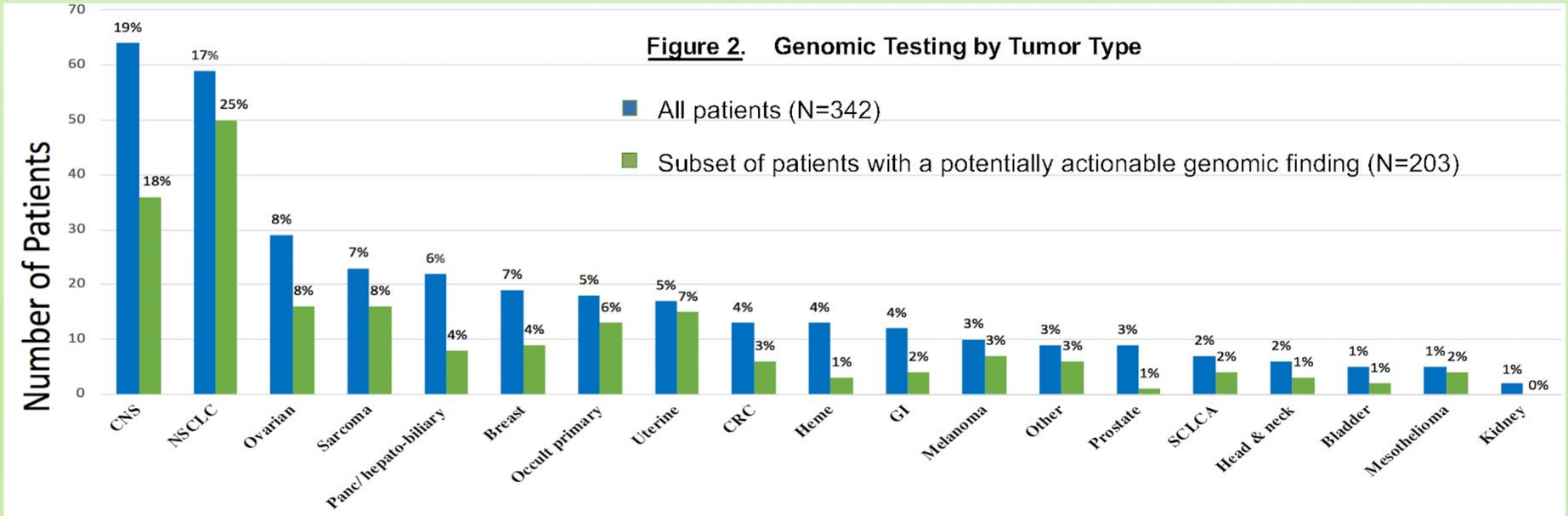


Table 1. Patients with actionable germline mutations by tumor type (N=11)

Tumor Type	Patients N (%)
Ovarian	3 (27%)
CNS	2 (18%)
Breast	2 (18%)
Pancreatic and hepatobiliary	1 (9%)
Endometrial	1 (9%)
Melanoma	1 (9%)
Prostate	1 (9%)

Figure 2. Genomic Testing by Tumor Type



Conclusions

- 59% (95% CI: 54-64%) of patients had potentially actionable mutations, but the majority of these individuals did not undergo germline testing
- Nearly 20% patients who underwent genetic testing were positive for germline mutations, with significant implications for patient treatment and screening

Next steps

- Follow-up of individuals with potential germline mutations
- Patient and provider education of the germline impact of genomic testing

Reference

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Results of Genetic Testing: Colorectal Carcinoma

Results of Genetic Testing Among Patients Undergoing Surgery for Colorectal Carcinoma in a Community Hospital Setting

Karin Cole[1], Alex Jones[2]
1 Portland Surgical Associates, 2 Tufts University School of Medicine

Background: Most cases of colorectal cancer (CRC) occur sporadically, though heritable factors may contribute to 5-10% of cases. The most commonly recognized heritable syndrome associated with CRC is Lynch Syndrome (LS), characterized by germline mutations in DNA mismatch repair (MMR) genes. Germline mutations in other genes, including APC, MUTYH, and STK-11, are associated with less frequently observed syndromes.

Methods: A total of 162 patients who underwent surgical resection of the colon or rectum for a diagnosis of CRC between 2011 and 2020 were considered for the present analysis. Serum testing for germline mutations was conducted based on abnormal MMR protein testing, clinical suspicion for a heritable mutation, and patient preference. Prevalence of germline mutations was subsequently calculated.

Results: MMR protein testing was abnormal in 32 of 157 patients for which results were available. Based on this abnormal finding, 13 patients underwent serum testing for germline mutations. An additional 11 patients with unavailable or normal MMR testing underwent testing based upon clinical suspicion. The resultant prevalence of germline mutations in this population was found to be 10/162 (6.2%).

Compared with 152 patients with no mutation identified, patients with germline mutations were more likely to have right-sided tumors (70% vs. 39%) and were younger (59 vs. 66 years old at time of surgery).

Conclusions: The observed prevalence of germline mutations in this population was similar to previously reported values. Community surgeons need to be familiar with indications for genetic testing and management of results.

Results of Genetic Testing Among Patients Undergoing Surgery for Colorectal Carcinoma in a Community Hospital Setting

Alex Jones[1], Dana Greer, RN, BSN, OCN[2], and Karin Cole, MD, FACS[1,2]

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BACKGROUND

Colorectal cancer (CRC) is the third leading cause of cancer death worldwide[1]. While most cases of CRC are considered to occur sporadically, heritable factors may be identified in 20-30% of cases, with 5-10% of cases being specifically associated with a defined genetic syndrome[2]. Indeed, colon and rectal cancers represent a heterogenous group of malignancies with diverse molecular and genetic underpinnings. Interestingly, specific genetic alterations are associated with tumor site[3] and distinct tumor behaviors, which in turn informs prognosis and options for targeted therapies. In some cases, germline mutations give rise to familial cancer syndromes with increased lifetime risk of developing CRC. Most common among these are Lynch Syndrome (LS) and Familial Adenomatous Polyposis (FAP), characterized by mutations in mismatch repair (MMR) genes and the Adenomatous Polyposis Coli (APC) gene respectively. Recognition of patients with these and other, less common, syndromes is of particular importance, as future risk for patients and their family members can be subsequently stratified. While many hospitals have implemented a universal protocol to screen CRC tumor tissue for MMR protein deficiency, the decision to screen patients for inherited genetic alterations using next-generation sequencing techniques is more complex. Regulatory bodies such as the National Comprehensive Cancer Network (NCCN) have recently provided guidance on which patients with CRC should undergo such testing, and although rates of multigene panel testing are increasing, barriers such as education and insurance coverage limit the number of qualifying patients who actually undergo testing[4]. These barriers may be even more pronounced in the community hospital setting[5]. We hypothesize that the prevalence of germline mutations may be lower than expected in a community-based cohort due to these barriers and the potential for referral of younger, more complex patients to large specialty centers. As such, we aim to determine the prevalence of heritable genetic mutations among patients undergoing surgery for CRC in a community setting and to characterize the group of patients testing positive. In addition, we investigated the indications for testing in our patient population.

PATIENTS AND METHODS

Study type: Retrospective

Setting: Mercy Hospital, Portland, ME (148-bed community hospital)

Patients: A total of 162 patients who underwent surgical resection of the colon or rectum for a diagnosis of CRC between 2011 and 2020 were considered for the present analysis. Surgeries were performed by a single surgeon (KC) at Mercy Hospital in Portland, Maine.

Data collection: Data were abstracted from an institution-specific, prospectively maintained colorectal surgery database. The database is approved by the institutional IRB for research purposes and patients enrolled after the approval date gave informed consent. Data abstracted included basic demographics, patient comorbidities, cancer location and stage, MMR genetic testing results, and multigene panel testing results.

Patients were presented at the institution's multi-disciplinary cancer conference at the time of presentation or following surgery, at which time genetic testing considerations were discussed. Staining of tumor tissue for MMR proteins was routinely performed. Serum multigene panel testing for germline mutations was conducted based on abnormal MMR protein testing, clinical suspicion for a heritable mutation, and patient preference. Tumors with MMR deficiency reflexed to *BRAF* and *MLH1* promoter hypermethylation testing to determine whether this deficiency was somatic in nature. A chart review was subsequently conducted to assess whether patients would have met current NCCN criteria for multigene panel testing irrespective of the index cancer diagnosis. These patients are described as meeting diagnosis-independent criteria (DIC).

Statistical analysis: Descriptive statistics only were used in this study.

RESULTS

MMR protein testing was abnormal in 32 of 157 patients for which results were available. Based on this abnormal finding, 13 patients underwent serum testing for germline mutations (the remaining 19 patients were found to have BRAF mutation or MLH1 promoter hypermethylation and therefore did not qualify for panel testing based upon MMR status). An additional 11 patients with unavailable or normal MMR testing underwent serum testing based upon clinical suspicion. Hence, in total 24/162 (15%) of the total population with CRC and 13/32 (41%) of those with abnormalities on universal MMR deficiency screening underwent multigene panel testing. The resultant prevalence of germline mutations in this population was found to be 10/162 (6%) in the overall population with CRC, and 10/24 (42%) specifically in those undergoing multigene panel testing (Figure 1A). Compared with 152 patients who did not undergo serum testing or had negative results, patients with germline mutations were more likely to have right-sided tumors (70% vs. 39%) and were younger (59 vs. 66 years old at time of surgery)(Table1).

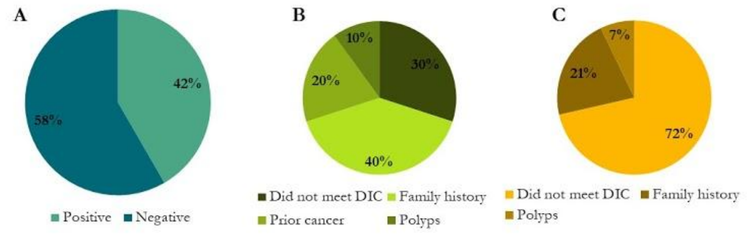

Figure 1: (A) Results of those undergoing multigene panel testing. Reasons for meeting diagnosis-independent criteria (DIC) for panel testing in those with (B) abnormal and (C) normal results.

A chart review revealed that of 24 patients undergoing multigene panel testing following diagnosis of CRC, 11 would have qualified based on other factors (i.e., met DIC). The reasons for qualification are displayed in Figure 1. Among those with abnormal panel testing results, 40% would have qualified based upon family history, irrespective of index CRC diagnosis. In those with normal panel testing, family history was still the most common reason for meeting DIC (21%), though a higher proportion of these patients would have no indication without index diagnosis when compared to the group with abnormal panel testing (72% vs 30%; Figure 1B/C).

Table 1: General and genetic tumor characteristics for all patients with abnormalities on multigene panel testing. MMR: mismatch repair; CRC: colorectal carcinoma; VUS: variant of uncertain significance

ID	Patient Age	Tumor Location	Tumor Stage	MMR Testing	Multigene Panel Result	Met Criteria without CRC	Reason for Meeting Criteria
1	62	Cecum	I	N/A	MUTYH x2	Yes	Polyps
2	63	Cecum	IIC	Abnormal	VUS in NBN	No	N/A
3	69	Cecum	I	Abnormal	MSH6	Yes	Prior Cancer
4	64	Right colon	I	Abnormal	VUS in ATM	No	N/A
5	68	Rectum	IIIB	Abnormal	MUTYH	No	N/A
6	43	Transverse colon	I	Abnormal	MLH1	Yes	Family History
7	64	Cecum	IIA	Abnormal	MUTYH Heterozygous	Yes	Family History
8	42	Cecum	IIA	Abnormal	PMS2	Yes	Prior Cancer
9	60	Transverse colon	IIC	Abnormal	MLH1/LYNCH	Yes	Family History
10	56	Right colon	IIIB	Normal	CHEK2	Yes	Family History

CONCLUSIONS

In our community-based cohort of patients undergoing surgery for colorectal cancer, the prevalence of identified germline mutations was 6%, within the range of previously reported values[2]. Among all patients with CRC in the present study, 15% underwent multigene panel testing. This value is slightly higher than another study among 4 academic centers, wherein 8.5% of patients with CRC underwent panel screening[6], suggesting that our patients did not face disproportionate barriers to testing, or else those barriers were addressed. The relatively high percentage of patients tested may be attributed to the routine discussion of cases with a genetic testing coordinator through multidisciplinary conference, or to the fact that this was a single-surgeon series, limiting variability in practice.

Patients found to have germline mutations were younger at the time of surgery than those not harboring such mutations, though were older than expected based on previously published data suggesting a mean age at diagnosis of less than 40 for those with germline mutations. It is also important to note, however, that just 1 in 5 patients diagnosed under the age of 50 carried such a mutation, suggesting a significant role for other factors[7] in the development of early onset CRC. Our finding may be due to small sample size, but may also better reflect the demographics of patients who present for care in a community setting. In either case, we believe it is important to consider heritable factors in all patients presenting with CRC regardless of age at diagnosis.

In the cohort of patients exhibiting germline mutations, 70% of cancers were right-sided compared to just 39% of those without such mutations. This is consistent with previous models that suggest a continuum of carcinogenesis along the gastrointestinal tract. In these models, right-sided tumors exhibit a higher degree of *BRAF* mutations and a higher degree of microsatellite instability[3]. This finding gives rise to the corollary that CRC cases characterized by heritable factors, and in particular those demonstrating microsatellite instability, are more likely to be right-sided. In our cohort, three patients demonstrating mutations associated with Lynch Syndrome and two with MUTYH mutations, corresponding to a related syndrome, each developed tumors in the transverse colon or cecum, consistent with this model. In our cohort, 46% of those undergoing multigene panel testing would have qualified for testing independent of CRC diagnosis. Interestingly, 30% of those who tested positive for a mutation would not have qualified, while the corresponding proportion among those who tested negative was 72%, suggesting that family history and other factors can predict some, but not all patients who will ultimately test positive. This underscores the importance of an approach to genetic counseling that is holistic in nature, but also dynamic and adaptable to changing personal history, family history, and guidelines. Limitations of this study include its retrospective nature, small sample size, and single-surgeon/single-institution population, which limits generalizability.

In conclusion, we demonstrated the prevalence of germline mutations among our community-based cohort of patients undergoing surgery for CRC is similar to previously published population-wide values. Patients with germline mutations were younger, more likely to have right-sided tumors, and could not always be identified by genetic testing criteria other than their index cancer diagnosis. Community-based oncology providers must remain cognizant of changing guidelines and advocate for systems-based practices that address limitations to implementing genetic counseling and screening. This will become increasingly important as targeted therapies and personalized medicine become more prevalent.

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The Effect of Extended Panel Molecular Testing

The Effect of Extended Panel Molecular Testing on Treatment Decisions for Patients with Lung, Breast and Colon Cancer.

Sara Topalovic, Christian A. Thomas

New England Cancer Specialists

Background: Genomic tumor testing via extended panel molecular testing (EPMT) is utilized to treat cancer patients with “targeted therapy” but testing is not always performed. We investigated which patients with stage IV lung, breast or colon cancer underwent EPMT and whether their test result did or did not change treatment decisions.

Methods: From 2016-2020 1,010 patients with stage IV lung, breast or colon cancer at NECS were analyzed: EPMT result available (Y/N), EPMT result (tier I-III), therapy directed by EPMT (Y/N), and reasons why EPMT-directed therapy was not initiated.

Results: EPMT results were available for 296 patients (29.3%). EPMT use increased over time as did the proportion of patients undergoing cell free DNA testing: 2016/17: 12 (tissue 8, cell free DNA 4); 2017/18: 69 (tissue 58, cell free DNA 11); 2018/19: 96 (tissue 71, cell free DNA 25); 2019/20: 180 (tissue 116, cell free DNA 64). 21.5% (n=45) of lung cancer patients, 24% (n=12) of the breast cancer patients and none of the colon cancer patients received EPMT directed therapy. Reasons for patients to not receive EPMT directed therapy were:

1. no actionable results: 103 (43.1 %).
2. receiving standard of care treatment: 46 (19.2%).
3. performance status inadequate: 36 (15.1%).
4. actionable mutation discovered but not acted upon: 35 (14.6%).
5. clinical trial eligible: 13 (5.4%).
6. targeted therapy declined by patient: 6 (2.5%).

Conclusions: The use of EPMT has increased over time, in part because of cell free DNA testing. EPMT results have the potential to change treatment recommendations but they are only available in a fraction of patients and many obstacles remain preventing patients from receiving EPMT-directed therapy. Strategies to improve EPMT utilization for all eligible patients and to support implementation of EPMT directed therapy are needed.

The Effect of Extended Panel Molecular Testing on Treatment Decisions for Patients with Lung, Breast and Colon Cancer.

Christian A. Thomas M.D and Sara Topalovic

NEW ENGLAND Cancer Specialists

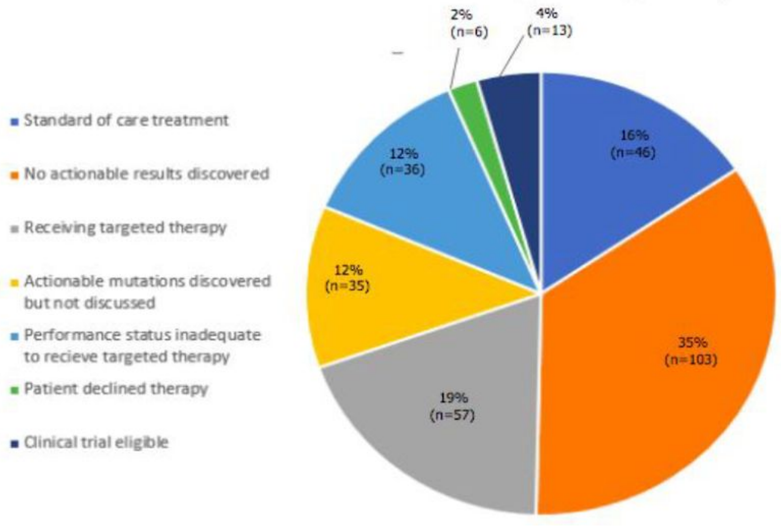
Introduction

Extended Panel Molecular Testing (EPMT) are increasingly utilized in clinical practice to detect potentially actionable mutations for which targeted treatments exist, thereby expanding therapeutic options for patients with advanced malignancies, especially when standard treatments are no longer effective. However, most EPMT results do not lead to a change in treatment and only 26.8% of oncologists reported EPMT results to be useful in making a treatment decision that affected patient care[1]. Here, we reviewed how EPMT results were utilized in patients with advanced breast, lung or colon cancer at a medical oncology Clinic (New England Cancer Specialists in Scarborough, ME). We sought to determine how often EPMT results lead to a change in therapy and analyzed reasons which precluded a therapeutic change for patients with a potentially actionable result.

Objective

The objective of the study is to determine the impact of EPMT results on patients with metastatic breast, colon, and lung cancer, by discovering the number of EPMT conducted and the effect the results have on patient's treatment plans.

Figure 1: Discoverable Test Results for Patients with Metastatic breast, colon, and lung cancer (n=296)



Methods

1,010 patients with stage IV lung, breast or colon cancer at NECS from 2016-2020 were analyzed with the following criteria: EPMT result available (Y/N), EPMT result (tier I-III), Therapy directed by EPMT (Y/N), and reasons why EPMT-directed therapy was not initiated. All data was recorded on Excel.

Results

Over the course of four years, 245 patients with breast cancer, 200 patients with colon cancer, and 565 patients with lung cancer were reported. Of the 1010 patients, 296 patients were found to have completed molecular test results; 36.6% (n=207) lung cancer patients, 20.0% (n=49) breast cancer patients, and 20.0% (n=40) colon cancer patients. Of the discoverable test results, 21.7% (n=45) of lung cancer patients received targeted therapy. 24.5% (n=12) of the breast cancer patients received targeted therapy, and none of the patients with colon cancer received targeted therapy. The patients that received no targeted therapy or trial following their discoverable results were divided into the appropriate categories, as shown in Figure 1.

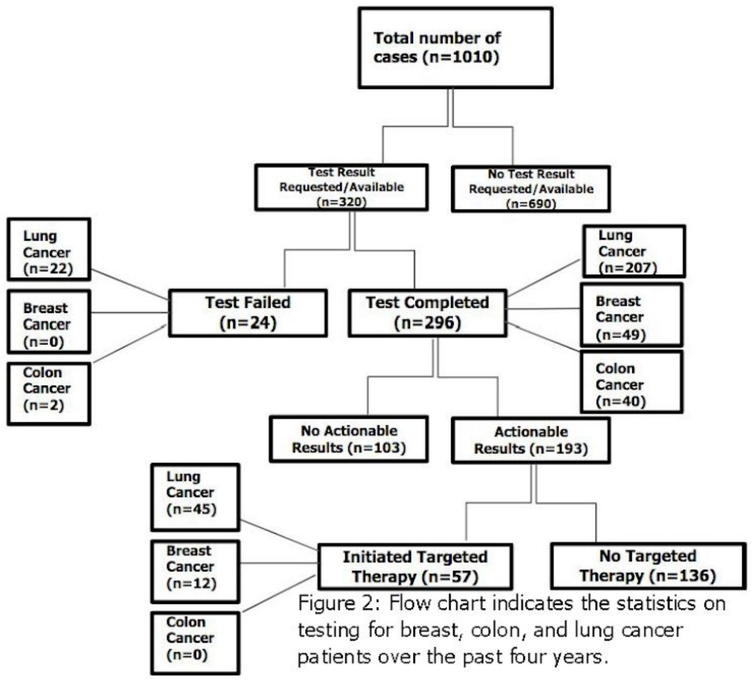


Figure 2: Flow chart indicates the statistics on testing for breast, colon, and lung cancer patients over the past four years.

Conclusions

There has been a rise in molecular testing and targeted therapies at New England Cancer Specialists from 2016-2020. The percentage of both lung and breast cancer patients receiving EPMT results, and targeted therapy has increased exponentially in the last year. This upward trend is likely due to an increase in cell free DNA testing. Both tissue and blood testing have become more frequent in the past four years (Figure 3). Although colon cancer patients have not received targeted therapy, molecular testing has increased. For those with actionable results that did not receive targeted therapy, there are a variety of confounding variables that still prevail and prevent patients from receiving or accessing targeted therapies or trials (Figure 1). We hypothesize that there will continue to be a gradual increase in molecular testing, leaving more options for patients that can no longer support standard of care treatment.

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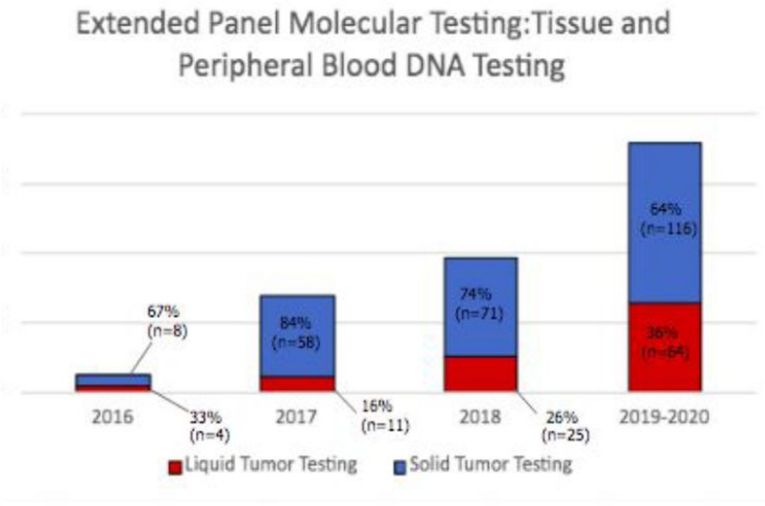

Figure 3: Bars indicate the ratio of liquid to solid tumor testing performed for patients with available molecular test results.

A bleeding tendency of the 8th degree

A bleeding tendency of the 8th degree- A case of Acquired Hemophilia A

Odeth Barrett-Campbell, Monic Drescher

Dartmouth-Hitchcock Medical Center

Background: Acquired hemophilia A (AHA) is a rare, but serious bleeding disorder with high mortality rates caused by the presence of autoantibodies to factor VIII (FVIII) and occurs later in life. Lack of awareness of the condition may delay diagnosis and lead to life-threatening bleeding.

Methods: Case presentation

Results: An 82 year old man with CVA on aspirin and aortic stenosis presented to the Hemophilia Clinic with a 1 month history of spontaneous sublingual hematoma, large ecchymosis on his legs, rectal bleeding and hematuria. Labs revealed normal PT, prolonged PTT, low FVIII activity level (11%, normal 50-150%) and high FVIII inhibitor level (11.2, normal <0.40 BU), which confirmed diagnosis of AHA. FIX, FXI and von Willebrand levels were normal. CT chest/abdomen/pelvis was normal. He received a 4 week course of Rituximab with clearance of the inhibitor and resolution of bleeding. Colonoscopy and cystoscopy were performed without bleeding complication. Cystoscopy was notable for a bladder stone attached to nodular enlarged prostate. Cystolitholapaxy and prostate biopsy are now planned.

Conclusions: It is crucial for early recognition of AHA given risk of spontaneous severe bleeding from the mucosa or soft tissue. Most cases are idiopathic but there is need to rule out autoimmune disorders or malignancies. The management entails a 2 step approach: 1. To control bleeding with agents such as FVIII inhibitor bypassing activity or recombinant FVIIa 2. To eliminate the inhibitor with rituximab, cyclophosphamide, steroids or combination. Once remission is achieved, although rare, there is a risk of recurrence. A routine follow-up and screening with aPTT prior to any invasive procedure should be considered.

A bleeding tendency of the 8th degree- a case of Acquired hemophilia A

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Introduction

- Acquired hemophilia A (AHA) is a rare, but serious bleeding disorder with high mortality rates
- It is caused by the presence of autoantibodies to factor VIII (FVIII) and occurs later in life
- Lack of awareness of the condition may delay diagnosis and lead to life-threatening bleeding
- We report a case report of AHA to increase awareness of this condition

Clinical presentation

- An 82 year old man with history of stroke on aspirin, aortic stenosis presented with one month history of spontaneous sublingual hematoma, large ecchymosis on his legs, rectal bleeding and hematuria
- Initial labs revealed anemia, normal PT and prolonged aPTT. which prompted referral to our Hemophilia Clinic
- Further work up showed low FVIII activity level (11%, normal 50-150%) and high FVIII inhibitor level (11.2, normal <0.40 BU)
- FIX, FXI and von Willebrand levels were normal. Lupus anticoagulant was negative
- To identify a potential cause of AHA, he underwent CT chest/abdomen/pelvis which revealed no evidence of malignancy
- A hemostatic agent was not administered given spontaneous improvement of his bleeding
- He received a four week course of Rituximab with clearance of the inhibitor and resolution of bleeding
- After eradication of the FVIII inhibitor, colonoscopy and cystoscopy were performed without bleeding complication
- Cystoscopy was notable for a bladder stone attached to nodular enlarged prostate. Cystolitholapaxy and prostate biopsy are now planned

Results

PT	**Normal**
aPTT	**Prolonged**
Factor VIII activity	**Low**
Factor VIII inhibitor level	**Elevated**

Discussion

- Factor VIII is the most common factor affected by autoantibodies
- Pathophysiology is unclear but may involve the presence of gene polymorphisms such as HLA, CTLA4 and/or autoreactive CD4+ T lymphocytes
- Most cases of AHA are idiopathic but there is need to rule out underlying autoimmune disorders, malignancies or drug reactions
- Hallmark of this condition is soft tissue or mucosal bleeding. Spontaneous hemarthroses as seen in hereditary factor VIII deficiency is unusual
- Management involves a two step approach:
  1. To control bleeding which may achieved by hemostatic agents such as FVIII inhibitor bypassing activity, recombinant FVIIa, factor VIII concentrates and desmopressin
  2. To eliminate the inhibitor by using immunosuppressive treatment either with rituximab, cyclophosphamide, steroids or combination

Take away points

- It is crucial for early recognition of AHA given risk of spontaneous severe soft tissue or mucosal bleeding
- Once remission is achieved, there is a risk of recurrence but this is rare
- A routine follow-up and screening with aPTT prior to any invasive procedure should be considered

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Immunotherapy related cardiotoxicity

A stun to the heart- a case of immunotherapy-related cardiotoxicity

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Background: Immune checkpoint inhibitor (ICI)-related cardiotoxicity is uncommon, but the expansion of immunotherapy will likely lead to more cases. It can have a fulminant course with a case fatality rate of up to 50%, which highlights need for early recognition.

Methods: Case Report

Results: A 60 year old man with advanced small cell carcinoma, most recently treated with cycle 2 of nivolumab, presented following an episode of diaphoresis, hypotension, and chest pain in the context of 3 weeks of dyspnea, orthopnea, palpitations and fatigue. He was admitted for NSTEMI as troponin was elevated. Echo showed a normal ejection fraction and no wall motion abnormalities. He was taking prednisone 40mg daily for presumed pneumonitis, however CT chest was negative for parenchymal changes or pulmonary embolism. Cardiac MRI was notable for delayed gadolinium enhancement in the epicardial region of the mid septum and inferior wall, in keeping with myocarditis. Coronary CT did not reveal obstructive coronary artery disease. He received methylpred 1g/day for 3 days with improvement in symptoms and decline in troponin. He was discharged on a tapering dose of prednisone.

Conclusions: The presentation is of ICI-induced myocarditis is variable but can have a rapidly deteriorating course. The onset is usually within 1 month of starting treatment or after 2-3 cycles, consistent with this patient's time- course. Combination immunotherapy increases the risk of cardiotoxicity and has an earlier onset of symptoms (12-15 days). Treatment involves use of high dose steroids and permanent discontinuation of immunotherapy. Mycophenolate, infliximab or anti-thymocyte granulocyte may be added to refractory cases.

A Stun to the Heart – A Case of Immunotherapy-Related Cardiotoxicity

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INTRODUCTION

- Immune checkpoint inhibitor (ICI)-related cardiotoxicity is uncommon, but the expansion of immunotherapy will likely lead to more cases
- It can have a fulminant course with a case fatality rate of up to 50%, which highlights need for early recognition

BACKGROUND

- Nivolumab is PD-1 blocking antibody that enhances immune system response to malignancy
- The incidence of ICI-related myocarditis ranges from 0.1 to 1% and can be fulminant with a mortality rate of 25-50%
- Commonly presents ~30 days or 2-3 cycles of therapy initiation with a variety of possible cardiac findings:
  - Troponins elevated or normal
  - BNP elevated or normal
  - EKG may be normal or show conduction abnormalities
  - Echocardiogram may show reduced ejection fraction, wall motion abnormalities, diastolic dysfunction, right ventricle dysfunction, pericardial effusion, or normal
  - Cardiac MRI showing late gadolinium enhancement (gold standard noninvasive test)
  - Endomyocardial biopsy with T cell invasion (gold standard)

CASE PRESENTATION

- A 60-year-old man with advanced small cell carcinoma, most recently treated with cycle 2 of nivolumab, presented following an episode of diaphoresis, hypotension, and chest pain in the context of 3 weeks of dyspnea, orthopnea, palpitations and fatigue
- He was taking prednisone 40mg daily for presumed pneumonitis, however CT chest was negative for parenchymal changes or pulmonary embolism

Hospital Course

- He was admitted for NSTEMI as troponin was elevated. Echo showed a normal ejection fraction and no wall motion abnormalities
- Cardiac MRI was performed and notable for delayed gadolinium enhancement in the epicardial region of the mid septum and inferior wall, in keeping with myocarditis. Coronary CT demonstrated no obstructive coronary artery disease

Treatment and Discharge

- He received methylprednisolone 1g/day for 3 days with improvement in symptoms and decline in troponin. He was discharged on a tapering dose of prednisone
- Discharge planning included close follow up of troponins to trend cardiac injury

DISCUSSION

- This patient's presentation is consistent with the timeline of myocarditis presenting after cycle 2 of treatment
- Fortunately, this patient had a mild case of myocarditis. This may be due to his single agent treatment, as combination immunotherapy increases the risk of cardiotoxicity and has an earlier onset of symptoms (12-15 days)
- He received high dose steroids and immunotherapy was discontinued. Other treatments could include mycophenolate, infliximab or anti-thymocyte granulocyte

NEXT STEPS

- Monitoring for cardiac signs of ICI adverse events crucial for preventing fulminant myocarditis
  - Consider screening EKG and troponins after 2-3 cycles of therapy
- Further research needed to establish risk factors for ICI-related myocarditis
- Possible role for CTLA-4 agonist, abatacept, in glucocorticoid refractory cases to cause rapid T cell anergy and decreased inflammation
- Patients with a history of ICI-associated myocarditis should have ongoing cardio-oncology care

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Hemolysis and Thrombocytopenia

A Case of Hemolysis and Thrombocytopenia Associated with Human Babesiosis in an Immunocompromised Host

Simrun Bal, Odeth Barrett-Campbell

DHMC

Background: Human babesiosis represents an emerging health risk in a variety of geographic regions, with an incidence that has been increasing in the northeastern US, where Babesia microti is endemic. The presentation can be variable depending on immune status, ranging from asymptomatic infection to severe disease, with complications such as ARDS, DIC, or renal failure which highlights the need for early recognition and treatment.

Methods: Case Presentation:

A 73-year-old woman with primary adrenal insufficiency presented with a 3 day history of fever, night sweats and malaise. She denied recent travel, but her daughter, a veterinary technician, had recently been ill with similar symptoms. Exam was notable for mild scleral icterus and diffuse ecchymoses over the arms. Labs demonstrated thrombocytopenia (39K), indirect hyperbilirubinemia and elevated AST. A peripheral smear revealed basophilic intra-erythrocytic inclusions suggestive of a parasite involving ~6% of total erythrocytes along with schistocytes. Babesia/Malaria testing of the peripheral smear was positive. Lyme disease or anaplasmosis were ruled out. Babesia microti antibody testing was still pending at time of report.

Results: Clinical improvement was noted with prompt initiation of azithromycin 500 mg daily and atovaquone 750 mg twice daily, as well as stress-dose steroids in the setting of adrenal insufficiency. A repeat peripheral smear is planned to assess for improvement in parasite load.

Conclusions: Thrombocytopenia with markers of hemolysis can produce a wide differential diagnosis. In an endemic geographic area such as the northeastern US, it is crucial to consider tick-borne illnesses such as babesiosis, particularly who are immunocompromised. This clinical vignette demonstrates a rare presentation of human babesiosis in a host at risk for significant decline, but who, with prompt treatment with azithromycin and atovaquone, had resolution of her signs and symptoms of babesiosis.

A Case of Hemolysis and Thrombocytopenia Associated with Human Babesiosis in an Immunocompromised Host

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Learning Objectives

1. Recognize the classic symptoms and sequelae of human babesiosis
2. Understand the pathophysiology of babesia infection
3. Learn about treatment strategies for babesiosis

Introduction

- Human babesiosis represents an emerging health risk in a variety of geographic regions.
- Incidence of human babesiosis has been increasing in the northeastern US, where *Babesia microti* is endemic.
- Typical presentation can be variable depending on one's immune status, ranging from asymptomatic infection to severe disease, with complications such as ARDS, DIC, or renal failure.

Case Presentation

- **A 73-year-old woman with primary adrenal insufficiency presented with a three-day history of fever, night sweats, rhinorrhea and malaise, accompanied by diffuse weakness.**
- Tmax 100.4F at home
- 1 daughter with similar symptoms, but not as severe
- No recent travel. Denied tick bites. Has one cat and one dog.
- Hx of long-standing primary adrenal insufficiency
- Attempted to treat herself with 40 mg IM methylprednisolone due to hx of primary adrenal insufficiency, no improvement in symptoms
- ROS: +Easy bleeding and bruising; negative for sore throat, cough, c/p, pressure.
- Exam was notable for stable vitals, Cushingoid appearance, icteric sclera with palatal jaundice of the oropharynx, and diffuse ecchymoses with petechiae. No meningismus was noted and CN II – XII were intact without any neurological deficits.
- Labs were notable for thrombocytopenia (Plt **36,000**), mild hepatocellular transaminitis (AST **48**, ALT **52**, Alkaline Phosphatase 68), indirect hyperbilirubinemia (TB **13.3**, DB **0.6**). The patient's rapid COVID test was negative.

Further Diagnostic Studies

Infectious Studies

Studies	
Anaplasma Phagocytophilum IgG and IgM	Not detected
Anaplasma Phagocytophilum DNA PCR	Not detected
Lyme Disease IgG and IgM	Not detected
Malaria/Babesia Exam	**Abnormal: Babesia sp. Seen, with parasitemia = 2.3%**
Babesia microti DNA PCR	**Detected**
Babesia microti Antibodies	**IgG: 1:256 (H)** **IgM: 1:160 (H)**

Patient's Peripheral Smear

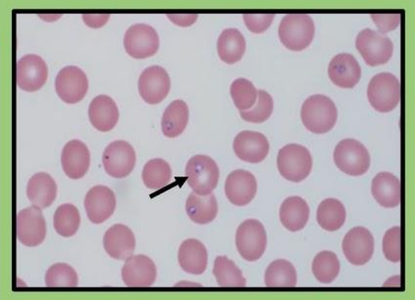

Fig. 1: Patient's peripheral smear
- Anisopoikilocytosis is minimal, polychromasia is moderate
- Ovalocytes and basophilic stippling are rare. Spherocytes are occasional.
- Frequently, RBCs contain round, fairly uniform basophilic inclusions (arrow)
- Neutrophils show toxic granules and Dohle bodies.
- Lymphocytes and monocytes show normal morphology.
- Comment: The RBC inclusions are suggestive of a parasite, most likely babesia. Spherocytes are present, as are seen with hemolysis, but not in marked numbers. Current infected RBCs estimated as < 10%.

Hospital Course

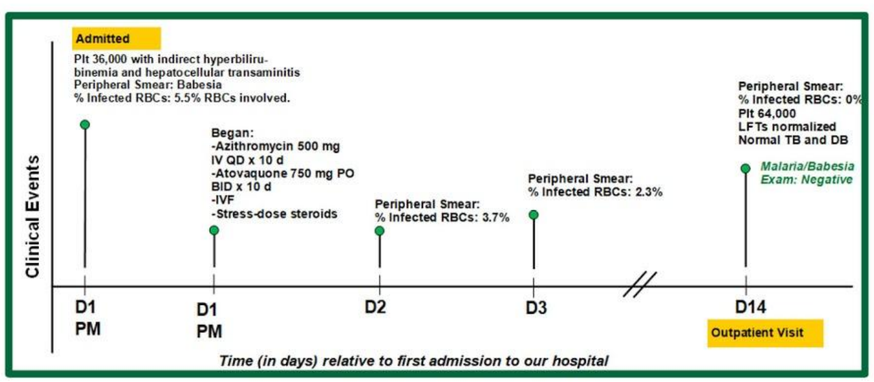

Fig. 2. Patient's clinical course and notable treatment decisions
The patient was promptly begun on a 10-day course of azithromycin and atovaquone. She also received IV hydration and was begun on stress-dose steroids in the setting of primary adrenal insufficiency.
Abbreviations and Symbols: Plt – platelet count, RBCs – red blood cells, QD – once per day, BID – twice per day, IVF – IV fluids; / / - more than two days passed

Discussion

- Thrombocytopenia with markers of hemolysis (such as hyperbilirubinemia) produces a wide differential diagnosis.
- In an endemic area such as the northeastern United States (Fig. 2), it is crucial to consider tick-borne illnesses, particularly in those who are immunocompromised.
- The causative agent of babesiosis is *Babesia microti*, and the vector is the *Ixodes scapularis* tick. Most cases are due to exposure to nymphal ticks (late spring to summer); high prevalence of ticks infected w/*B. microti* in southern New England (1,2).
- *B. microti* sporozoites attach to erythrocytes → mature into trophozoites → form merozoites → host erythrocyte ruptures, other erythrocytes are invaded. Spleen clears infected RBCs and mounts an immune response (1).
- Symptoms can vary: subclinical infection to fulminating disease. Severity depends on immune status of patient. Typical: malaise, fatigue, fever, chills, sweats. Exam can be notable for splenomegaly, pharyngeal erythema, hepatomegaly, jaundice (1).
- Labs in babesiosis demonstrate signs of hemolytic anemia, thrombocytopenia; can have asymptomatic parasitemia lasting for months, with relapse a possibility in immunocompromised patients. IgG titers for babesia antibody > 1:1024 during acute phase of illness (1).
- Peripheral smear: trophozoites can appear as pleomorphic ring forms, sometimes in a "Maltese cross" pattern (3) (Fig. 3).
- Tx: Atovaquone, Azithromycin; if severe illness – IV Clindamycin with oral quinine. If high level of parasitemia or renal or hepatic compromise – can consider exchange transfusion (1).

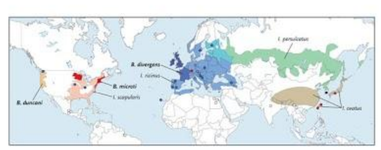

Fig. 2. Areas of endemic babesiosis and *Ixodes* tick vectors. Light colors are where the *Ixodes* vector is endemic, but no documented babesiosis. Dark areas – where babesiosis is endemic (solid) or sporadic. See Ref. 1.

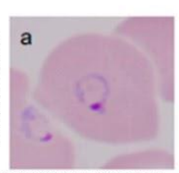

Fig. 3. *B. microti* infection of RBCs. Trophozoites can be in ring forms (a).
Source: Bloch EM, Kumar S, and Krause PJ. Persistence of *Babesia microti* infection in humans. *Pathogens* 2019 (8), 102.

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Radiation-Associated Cutaneous Angiosarcoma

A Case of Radiation-Associated Cutaneous Angiosarcoma Development After Prior Breast Malignancy

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Background: Radiation therapy is an important part of cancer treatment, with over 50% of patients receiving radiation for their disease. Secondary cancers are a rare but serious complication following radiation for primary malignancies. Approximately 5% of patients who receive therapeutic radiation will experience this secondary effect.

Methods: Case Report

Results: 64-year-old female with a history of infiltrative ductal carcinoma, ER+ PR + Her2-, was treated with lumpectomy, 4 cycles of adjuvant chemotherapy followed by endocrine therapy. Approximately 18 months post RT, she noticed blisters with associated pain within the mammary crease of her right breast. She underwent three biopsies and, per local reports, these were negative for malignancy but contained “lymphatic malformations related to radiation”. She underwent surgical breast reduction 11 months later. Surgical pathology reported the tissue demonstrated multifocal cutaneous angiosarcoma, arising in the background of extensive atypical post-radiation vascular proliferations. No evidence of metastatic disease on imaging. She received 4 cycles of bevacizumab, gemcitabine and paclitaxel and underwent radical resection of right breast sarcoma and overlying radiation field skin. She is followed yearly with surveillance imaging, no evidence of disease 10 years post initial diagnosis of cutaneous angiosarcoma.

Conclusions: Early detection of radiation-associated angiosarcoma is challenging. Predisposing risk factors are not well-defined with no clear or specific screening recommendations for patients who have undergone radiation other than those for surveillance of primary malignancy. Since mammographic findings are often non-specific, skin thickening is often the only relevant finding, however, it is difficult to differentiate dermal lesions from thickening secondary to radiation.

Case Report: Radiation-Associated Angiosarcoma Development After Prior Breast Malignancy

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BACKGROUND

Radiation therapy is used as an important part of cancer treatment, with more than 50% of all cancer patients receiving radiation at some point over their disease course. Secondary cancers are a rare but serious complication following therapeutic radiation for primary malignancies and approximately 5% of patients experience this serious secondary effect (1).

Radiation-associated sarcomas account for fewer than 1% of patients who receive radiation therapy, which represents up to 5% of all sarcomas. The use of radiation therapy has been increasing and with a growing population of cancer survivors the incidence of radiation-associated sarcomas is expected to rise (2).

Patients with carcinoma of the breast are the most common groups to receive radiation therapy as part of their primary malignancy treatment plan and who are at risk to subsequently develop radiation-associated sarcoma (2).

Angiosarcoma is an aggressive, malignant endothelial-cell tumor of lymphatic or vascular origin which represents <1% of all soft-tissue sarcomas (15). (Image 1).

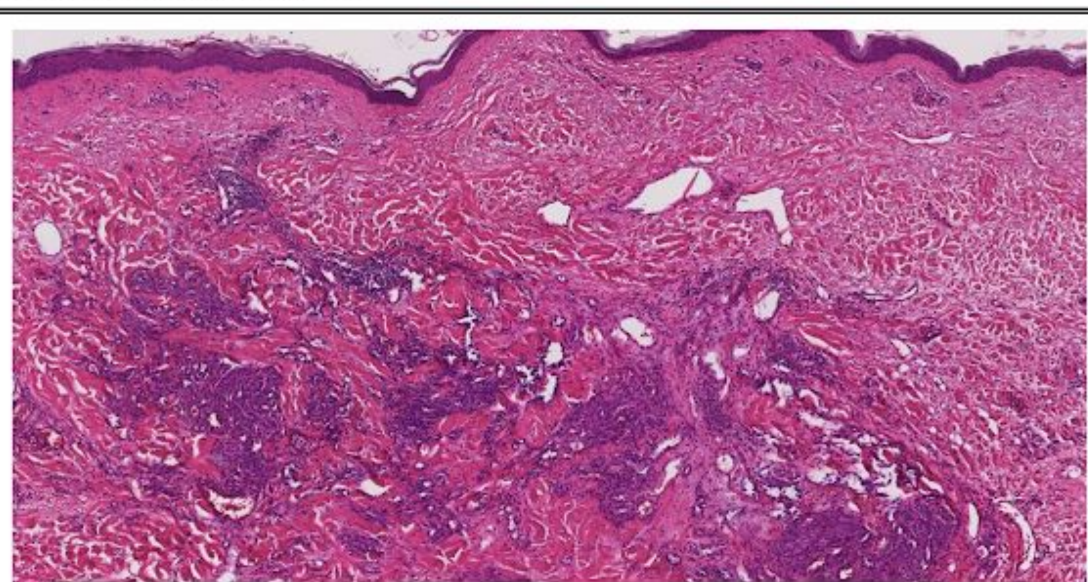


Image 2: Histology: Radiation-associated angiosarcoma of the breast
Anastomosing vascular channels infiltrating the dermis
http://www.pathologyoutlines.com/topic/breastmalignantangiosarcoma.html

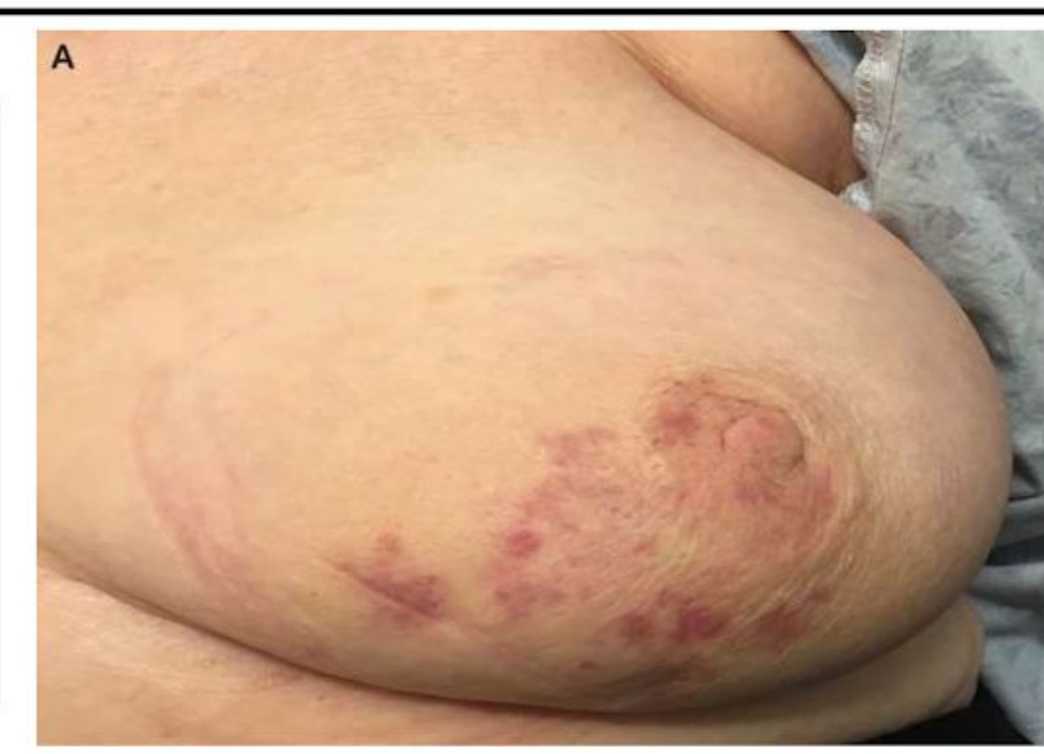
LITERATURE REVIEW

- Radiation-associated sarcomas are considered to have a poor prognosis (3). A recent study showed a 5 year overall survival rate of 68% with margin-negative excision, superficial tumor location and low tumor grade, suggesting that early detection and complete surgical excision are important for optimal treatment for radiation-associated sarcomas (4-5).
- The incidence of this rare disease has been explored in numerous studies. Consensus is in those patients undergoing breast conserving surgery with adjuvant radiotherapy, the estimated incidence of radiation associated angiosarcoma is between 0.05–0.3% (16, 18, 19, 28, 30,31).
- Median interval between breast irradiation and diagnosis of radiation induced angiosarcoma suggest a latency period ranging from 3 to 20 years (23, 28).
- Early detection of radiation-associated angiosarcoma is challenging. There are no clear or specific screening recommendations for patients who have undergone radiation other than those for surveillance of primary malignancy.
- A study by Guo et al. showed *MYC* amplification is one of the hallmarks of secondary AS and can be used as a molecular diagnostic tool to distinguish from other atypical vascular lesions or sarcoma types. (36).

CASE

- A 64-year-old female with a history of high grade infiltrative ductal carcinoma, ER+, PR +, Her2-, was treated with lumpectomy, 4 cycles of adjuvant chemotherapy with docetaxel plus cyclophosphamide and post-surgical radiation of 33 fractions followed by endocrine therapy.
- 18 months post RT, she noticed blisters with associated pain within the mammary crease of her right breast. She underwent three separate biopsies and, per local pathology reports, these were negative for malignancy but contained "lymphatic malformations likely related to radiation".
- She then underwent surgical breast reduction 11 months later. Surgical pathology reported tissue demonstrated multifocal cutaneous angiosarcoma with focally epithelioid features, arising in the background of extensive atypical post-radiation vascular proliferations.
- Chest, abdomen and pelvis CT showed no evidence of metastatic disease.
- She received 4 cycles of bevacizumab, gemcitabine and paclitaxel and then underwent radical resection of right breast sarcoma with resection of overlying breast skin.
- Pathology showed no residual cutaneous angiosarcoma within the right breast or axillary tissue with negative lymph nodes.
- She was followed with repeat chest, abdomen and pelvis CT with chest wall MRI every 3 months for the first-year post surgery, transitioning to every 6 months until 5 years post-surgery. She is now followed yearly with surveillance imaging and exam and no evidence of disease 10 years post initial diagnosis of cutaneous angiosarcoma.

Image 1: Examination reveals an area of skin that had an ecchymosis appearance, with no underlying mass or nodular tissue. Secondary, radiation associated angiosarcoma often presents with skin changes, typically in older patients (median age 70). Primary angiosarcoma presents as a palpable mass in younger patients (median age 40). https://www.nejm.org/doi/full/10.1056/NEJMicm1516482?query=recirc_inIssue_bottom_article



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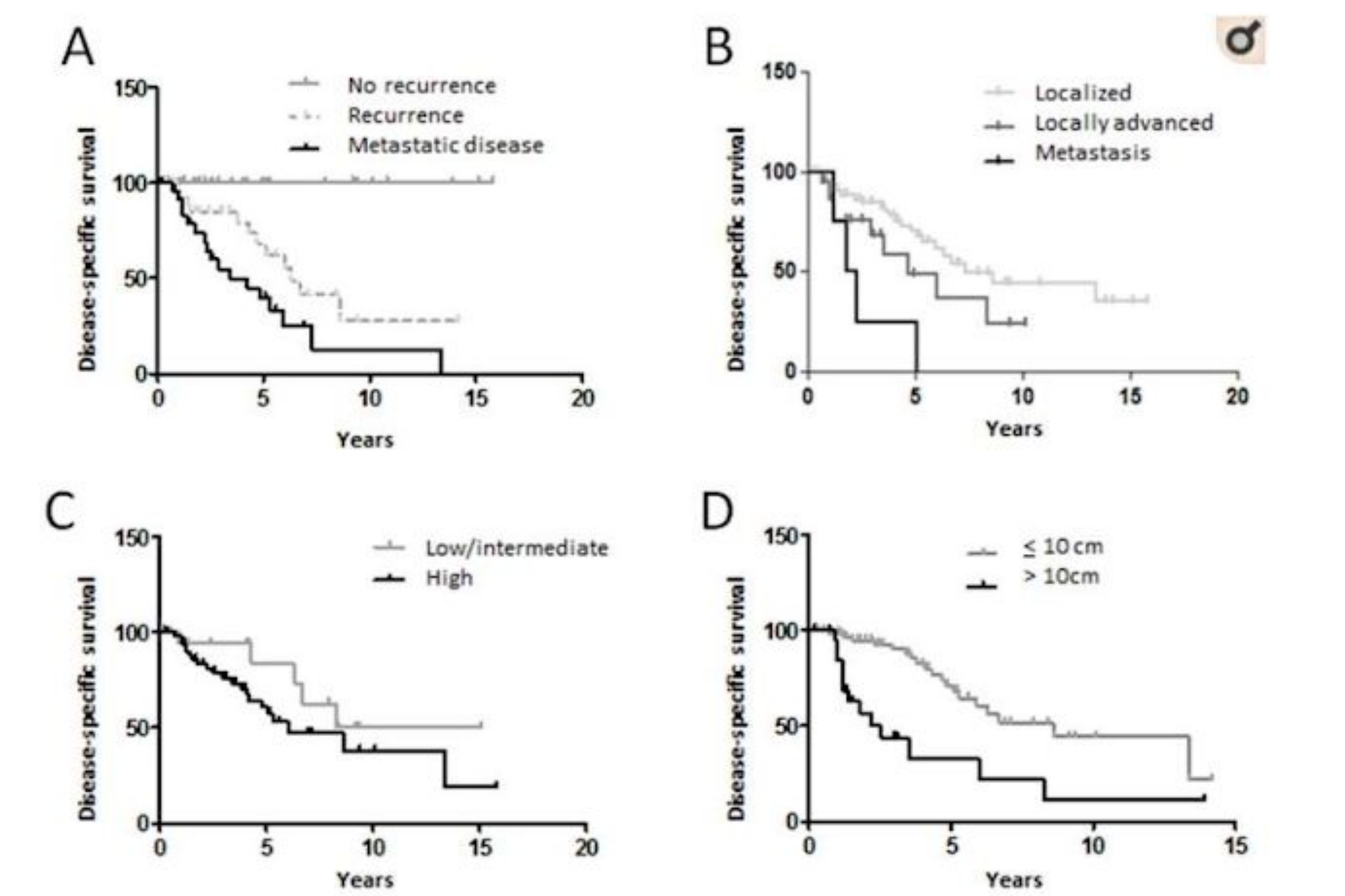

Figure 1: Torres Kem et al. (28) Kaplan-Meier survival curves for angiosarcoma-specific survival for: **A**, Patients that did not develop recurrence versus recurrence only versus metastatic disease, $P = 0.0002$; **B**, Localized versus locally advanced versus metastatic, $P = 0.01$; **C**, Low/intermediate grade versus high grade, $P = 0.2$; **D**, Size $\leq$ 10cm versus > 10 cm, $P = 0.005$

DISCUSSION AND CONCLUSIONS

- There may be a significant time lapse between patient presentation with cutaneous changes and diagnostic biopsy.
- Predisposing risk factors for the development of radiation-associated sarcomas are not well defined.
- It is becoming increasingly clear that hereditary predispositions genes are more common than previously thought in patients who develop malignancy.
- With advances in next-generation DNA sequencing technology, testing for multiple genes associated with hereditary susceptibility to cancer is now possible.
- There is benefit to identifying a cancer predisposition syndrome including identification of future cancer risk and options for screening and prevention.
- While the availability of testing has grown, the identification of new hereditary predisposition genes has been complicated by lack of clinical information linked to patient mutation status.
- The collection and analysis of research specimens collected from radiation-associated sarcoma patients from Dana-Farber Cancer Institute and Brigham and Women's Hospital, conducted through the PROACTIVE study, aims to identify those at risk of developing radiation associated angiosarcoma.

Acknowledgements

I would like to acknowledge the sarcoma research team at Dana-Farber Cancer Institute for the opportunity to participate in a medical student research elective. I would especially like to thank Dr. Priscilla Merriam, for her clinical and research mentorship.

Refractory hemophagocytic lymphohistiocytosis

A case of refractory hemophagocytic lymphohistiocytosis and anaplastic DLBCL

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Dartmouth-Hitchcock Medical Center

Background: HLH is a disorder of uncontrolled immune activation and inflammation. It may be primary or secondary (driven by infection, malignancy, or autoimmunity) and has high mortality even with therapy.

Methods: A 54-year-old woman presented with 6 weeks of fatigue, fever, rash, and abdominal pain. Labs revealed pancytopenia and elevated ferritin, LDH, triglycerides, ESR, CRP, and sCD25. CT showed hepatomegaly and splenomegaly. Infectious work-up was negative. Bone marrow biopsy showed no hemophagocytosis.

Due to concern for adult-onset Still's disease/macrophage activating syndrome she was treated with prednisone and methotrexate. She improved, but symptoms recurred with steroid taper. Repeat marrow biopsy was unchanged.

She had multiple hospitalizations for symptom flares associated with cytopenias and elevated ferritin and received steroids and tocilizumab with rapid improvement. A third marrow biopsy showed hemophagocytic histiocytes, confirming HLH, and she started etoposide and dexamethasone with plan for allogeneic HSCT.

During chemotherapy she developed pulmonary embolism, lactic acidosis, and pancytopenia. She opted for comfort care and died 6 months after initial presentation.

Results: Autopsy revealed metastatic anaplastic DLBCL in the spleen, liver, lymph nodes, and kidneys. Bone marrow PCR testing for B-cell IgH and T-cell receptor gene rearrangements subsequently returned suspicious for clonality.

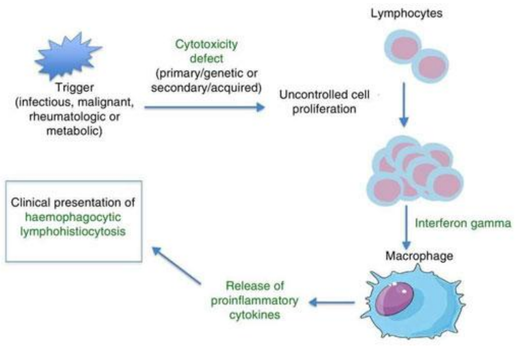
Conclusions: We describe a case of refractory HLH driven by DLBCL diagnosed on autopsy. Anaplastic DLBCL is a variant associated with an aggressive course and poor prognosis. This case illustrates an unusual presentation with no lymphadenopathy, and demonstrates the importance of maintaining high clinical suspicion for occult hematologic malignancy in cases of refractory HLH.

A Case of Refractory Hemophagocytic Lymphohistiocytosis and Anaplastic DLBCL

Allison Smith, MD, MPH; Elizabeth Bengtson, MD
Dartmouth-Hitchcock Medical Center, Department of Hematology/Oncology

Background

- HLH = disorder of uncontrolled immune activation and extreme inflammation
  - Primary: mutations in T- and NK-cells
  - Secondary: to infection, malignancy, autoimmunity



Astigarraga et al, An Pediatr, 2018

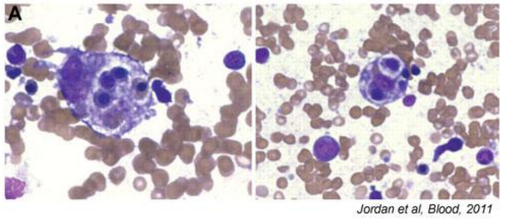
Case Report

- 54 year old woman presented with 6 weeks of fatigue, fever, night sweats, anorexia, rash, and abdominal pain
- Labs:
  - ❋ Pancytopenia: hemoglobin 8.7, WBC 2.8, platelets 78,000
  - ❋ Elevated ferritin (4941 ng/ml) and LDH (885 u/L)
  - ❋ Elevated triglycerides (564 mg/dL)
  - ❋ Elevated ESR (71 mm/hr) and CRP (82 mg/L)
- CT Abdomen/Pelvis: hepatomegaly, splenomegaly 17 cm with splenic infarct, no lymphadenopathy
- Extensive infectious work-up: negative
- Bone marrow biopsy x2: no hemophagocytosis
- High soluble CD25 (14,750 pg/ml)
- Concern for adult-onset Still's disease with macrophage activating syndrome/HLH
  - → treated with prednisone 1 mg/kg/day and MTX
  - → significant clinical improvement
  - → symptoms returned when steroids tapered

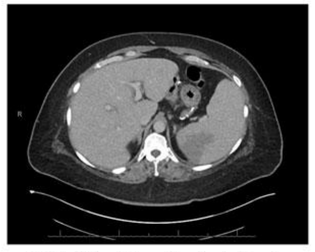
Case Report (continued)

- Multiple hospitalizations for symptom flares associated with cytopenias and elevated ferritin
  - → pulse steroids, tocilizumab → rapid improvement
- 3rd bone marrow biopsy: hemophagocytic histiocytes
  - ❋ Met 7/8 diagnostic criteria for HLH
  - ❋ H-score = 223 = 96.9% probability of HLH
- Started etoposide and dexamethasone with plan for allogeneic stem cell transplant
- During chemotherapy she was admitted with PE, lactic acidosis, and pancytopenia
  - → opted for comfort care
  - → passed away 6 months after initial presentation
- Autopsy: metastatic anaplastic DLBCL with large cells in spleen, liver, lymph nodes, bilateral kidneys
  - ❋ Sections of bone marrow from iliac crest, vertebrae, and rib showed no malignancy
- Subsequently received results for bone marrow PCR testing for B cell IgH and T-cell receptor gene rearrangements: suspicious for clonality

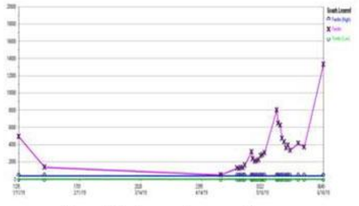
Hemophagocytic macrophages on bone marrow aspiration



Jordan et al, Blood, 2011



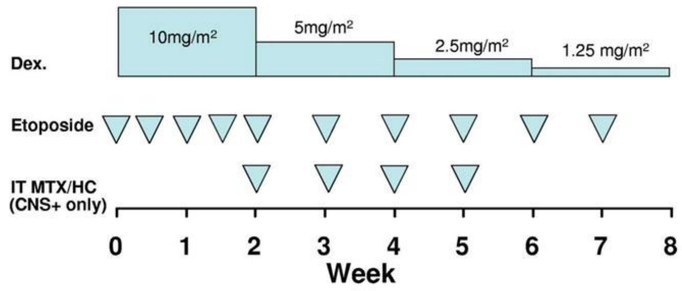
CT A/P with splenic infarct



Ferritin trend over time

HLH

Treatment Protocol for HLH (from HLH-94 Trial)



Diagnostic Criteria for HLH (from HLH-2004 Trial)

The diagnosis of HLH requires a molecular diagnosis consistent with HLH or 5 of 8 of the below criteria
1. Fever
2. Splenomegaly
3. Cytopenias affecting ≥2 lineages
a. Hemoglobin <9 g/dL
b. Platelets <100 × 10^9/L
c. Neutrophils <1.0 × 10^9/L
4. Hypertriglyceridemia and/or hypofibrinogenemia
a. Triglycerides ≥265 mg/dL
b. Fibrinogen ≤150 mg/dL
5. Hemophagocytosis in bone marrow, spleen, or lymph nodes
6. Low or absent NK cell activity
7. Ferritin ≥500 μg/L
8. sCD25 (ie, sIL2R) ≥2400 U/mL

Jordan et al, Blood, 2011

Conclusion

We describe a case of refractory HLH driven by metastatic anaplastic DLBCL diagnosed on autopsy. Anaplastic DLBCL is a variant associated with an aggressive clinical course and poor prognosis.

This case illustrates an unusual presentation of anaplastic DLBCL with no lymphadenopathy, and demonstrates the importance of maintaining high clinical suspicion for occult hematologic malignancy in cases of refractory HLH.

Acute myeloid leukemia

Acute myeloid leukemia with hepatic infiltration presenting as obstructive jaundice

Landis R. Walsh[1], Chaofan Yuan[2], James T. Boothe[2], Heather E. Conway[2], Andres E. Mindiola Romero[2], Odeth O. Barrett-Campbell[1,2], and Frederick Lansigan[1,2]

1 Geisel School of Medicine at Dartmouth, 2 Dartmouth-Hitchcock Medical Center

Background: Extramedullary manifestation of Acute Myeloid Leukemia (AML) is rare but confers a significantly worse prognosis. Most commonly it presents as myeloid sarcoma, but there have been reports of AML presenting as cholestasis with obstructive jaundice. In these cases, induction therapy is delayed for cholestasis workup due to concerns of chemotherapy toxicity exacerbated by liver dysfunction or concerns of untreated, concurrent cholecystitis progressing to sepsis in a severely neutropenic patient.

Methods: A 55-year-old woman presented with progressive right upper quadrant abdominal pain, jaundice, and laboratory workup concerning for acute leukemia. Her initial CBC showed a WBC 115.6 x103/uL and 60% peripheral blasts. Bedside ultrasound showed thickening of the gallbladder and pericholecystic fluid, and serum metabolic panel revealed transaminitis and cholestasis (total bilirubin 3.3mg/dL). Subsequent imaging including CT, HIDA scan, and MRCP indicated no biliary duct dilation, obstructive process, or choledocholithiasis, suggesting primarily hepatocellular injury rather than biliary tract pathology. Liver biopsy confirmed AML infiltration of the liver.

Results: Hydroxyurea was initiated as cytoreductive therapy during cholestasis workup and our patient's liver function improved with total bilirubin levels normalizing to 1.5mg/dL. Full-dose 7+3 induction with cytarabine and daunorubicin was then initiated. Bone marrow biopsy review at 14 and 30 days showed no residual leukemia, with significant hypocellularity noted at Day 30. She is currently being evaluated for allogeneic stem cell transplant with a goal of curative intent.

Conclusions: Our case highlights the utility of cytoreductive therapy as a rapid temporizing measure for hyperleukocytosis, providing important time for diagnostic workup prior to initiation of induction chemotherapy.

Acute Myeloid Leukemia Presenting as Obstructive Jaundice – the Race to Diagnosis

Landis R. Walsh[1], Chaofan Yuan, MD[2], James T. Boothe, MD[2], Heather E. Conway, MD[2], Andres E. Mindiola Romero, MD[3], Odeth O. Barrett-Campbell, MD[1,2,4], and Frederick Lansigan, MD[1,2,4]

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Abstract

The initial treatment for most cases of acute myeloid leukemia (AML) consists of early initiation of 7+3 induction chemotherapy (cytarabine + daunorubicin), though the presenting symptoms of AML can be varied. Here, we report a case of a 55-year-old woman who was admitted for progressive right upper quadrant abdominal pain, jaundice, and laboratory workup concerning for acute leukemia. Her initial CBC showed a WBC 115.6 x103/uL and 60% peripheral blasts. To prevent leukostasis complications, early hydroxyurea therapy was initiated for cytoreduction. Bedside ultrasound showed appreciable thickening of the gallbladder and pericholecystic fluid, and serum metabolic panel revealed transaminitis and cholestasis. However, subsequent advanced imaging including CT, HIDA scan, and MRCP (Figure 1-3) indicated no biliary duct dilation, obstructive process, or choledocholithiasis, suggesting primarily hepatocellular injury rather than biliary tract pathology. Hepatic biopsy (Figure 4) established AML infiltration of the liver and 7+3 induction was begun once total serum bilirubin levels decreased to 1.5mg/dL. This case demonstrates the potential for AML to infiltrate the parenchyma of major solid organs, resulting in atypical clinical and laboratory presentations, and furthermore it demonstrates the potential utility of cytoreductive therapy as a rapid temporizing measure for severe leukocytosis prior to initiation of induction chemotherapy.

Background

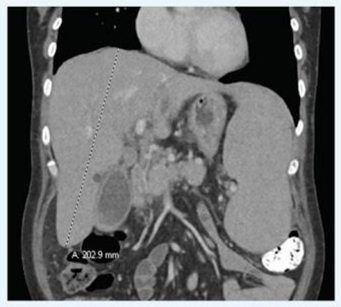
- Extramedullary manifestation of Acute Myeloid Leukemia (AML) is rare but confers a significantly worse prognosis [1,2]
- Most commonly it presents as myeloid sarcoma and there only have been few case reports of AML presenting as cholestasis with obstructive jaundice.
- Induction therapy is often delayed for cholestasis workup due to one of two reasons:[3,4]
  - Concerns of chemotherapy toxicity exacerbated by liver dysfunction
  - Concerns of untreated, concurrent cholecystitis progressing to sepsis in a severely neutropenic patient.

Patient Course

- A 55-year-old woman presented 3 week history of right upper quadrant abdominal pain, fevers, night sweats, gingival bleeding and swelling, and jaundice.
- Initial CBC: WBC 115.6 x10^3/uL and 60% peripheral blasts
- Initial Basic Metabolic panel: Elevated LFTs (AST 204/L and ALT 244/L), total bilirubin 3.3 mg/dL, direct bilirubin 2.5 mg/dL, and alkaline phosphatase 1082/L.
- Bedside ultrasound showed thickening of the gallbladder and pericholecystic fluid
- Subsequent imaging including CT, HIDA scan, and MRCP indicated no biliary duct dilation, obstructive process, or choledocholithiasis, suggesting primarily hepatocellular injury rather than biliary tract pathology

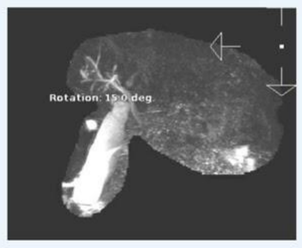
Imaging

CT abdomen with contrast

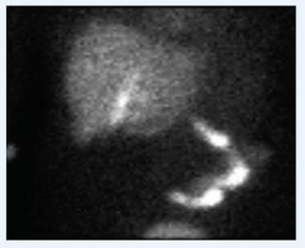


- Figure 1 (Left). Hepatomegaly appreciated (measuring 20.3 cm as shown by dotted line), with a likely cyst adjacent to the gallbladder. Gallbladder is distended with wall thickening, pericholecystic fluid and sludge within the gallbladder. Also show is splenomegaly, measuring 17.3 cm.

MRCP

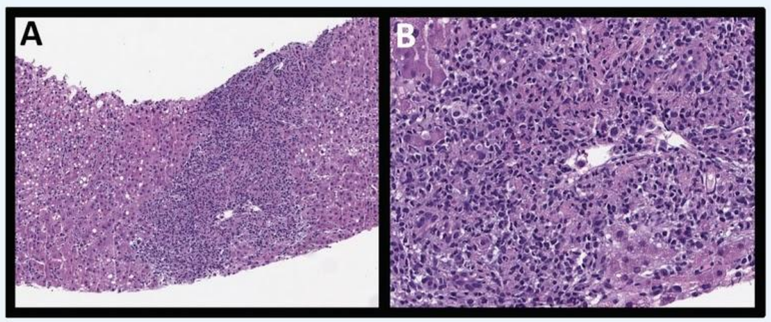


HIDA Scan



- Figure 2 (Above left). MRCP demonstrating sludge within a mildly dilated gallbladder with gallbladder wall thickening, without intrahepatic biliary dilation or extrahepatic biliary dilation.
- Figure 3 (Above right). HIDA scan, no evidence of acute cholecystitis. Shown is a still image of radiotracer being excreted from the liver (above) towards the proximal small bowel (not visualized)

Liver Biopsy (H&E stained)



- Figure 4A. Medium power view showing mild steatosis of the liver (sides) with a brisk portal and lobular infiltrate (center) (magnification x 40).
- Figure 4B. High power view showing an infiltrate comprised of atypical mononuclear cells along with bile duct proliferation and portal expansion with edema (original magnification x 200).

Management

- Patient was started on Hydroxyurea 2 grams q6hr and total bilirubin dropped to 1.3 mg/dL by hospital day 13.
- Full-dose 7+3 induction with cytarabine and daunorubicin was initiated once total bilirubin <1.5mg/dL
- Repeat bone marrow biopsy on day 14 and 30 revealed profound hypocellularity (<10%) and a small foci of early erythroid and granulocytic maturation and was still clear of residual leukemia.

Discussion

- Cholestasis in our patient was attributed to AML infiltration within the bile duct leading to acalculous cholestasis
- Hydroxyurea pretreatment provided temporization of hyperleukocytosis and concurrent cholestasis in this case
- Increased time for diagnosis provided time to rule out choledocholithiasis and acute cholecystitis
- Delayed induction of chemotherapy allowed for full dose induction therapy with successful response to treatment

Conclusion

Workup of obstructive jaundice in acute leukemia to rule out choledocholithiasis is challenging. Our case highlights the **utility of cytoreductive therapy as a rapid temporizing measure for hyperleukocytosis**, providing important time for diagnostic workup prior to initiation of induction chemotherapy.

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Primary cutaneous Diffuse large B cell lymphoma

Primary cutaneous Diffuse large B cell lymphoma leg type with bilateral Bells Palsy as initial presentation

Ximena Jordan Bruno, Julian Sprague

University of Vermont

Background: Primary cutaneous diffuse large B cell lymphoma leg type is an uncommon type of primary cutaneous lymphoma with an aggressive clinical course and usually suboptimal response to standard chemotherapy. Mostly affects females in their 7th or 8th decade of life and represents around 1 percent of all primary cutaneous B cell lymphomas.

Methods: 81 y old female with past medical history of atrial fibrillation on anticoagulation and hypertension who was admitted to the hospital in two opportunities with signs and symptoms consistent with bilateral Bells palsy and who was found to have a progressive right sided leg rash that was biopsied.

Results: Skin biopsy consistent with primary cutaneous diffuse large B cell lymphoma leg type

Conclusions: This presentation with bilateral Bells palsy has not been thus far described in the literature in association with a diagnosis of diffuse large B cell lymphoma leg type

PRIMARY CUTANEOS DIFFUSE LARGE B CELL LYMPHOMA, LEG TYPE, PRESENTING AS BELL'S PALSY

Ximena Jordan Bruno MD[1], Clayton LaValley MD[2], Laura Greene MD[2], and Julian Sprague MD PhD[1]

[1] Division of Hematology and Oncology, University of Vermont Medical Center, [2]Department of Pathology and Laboratory Medicine, University of Vermont Medical Center

Introduction

- Primary cutaneous diffuse large B-cell lymphoma, leg type, is a very uncommon and aggressive type of diffuse large B cell lymphoma (DLBCL)
- Paraneoplastic syndromes have been described in the clinical presentation of these patients
- Bilateral affection of the facial nerve is unique and as yet not described as a presentation for this lymphoma

Clinical Presentation

- 81-year-old woman presented with right sided facial droop, no associated pain or numbness; discharged from ED with information on Bell's palsy and PCP follow-up
- Presented 2 months later with left sided facial weakness, associated numbness and pain; Admitted with work up included lumbar puncture, MRI brain and MRI spine
- Skin biopsy was performed on day 3 of admission due to a rash (Image 1) that was present for 1 year
- Prelimin of DLBCL on day 7 of admission that was later confirmed as primary cutaneous diffuse large B cell lymphoma, leg type
- Staging PET body showed multiple soft tissue nodules in right leg and right inguinal node
- Staging bone marrow biopsy was negative for involvement

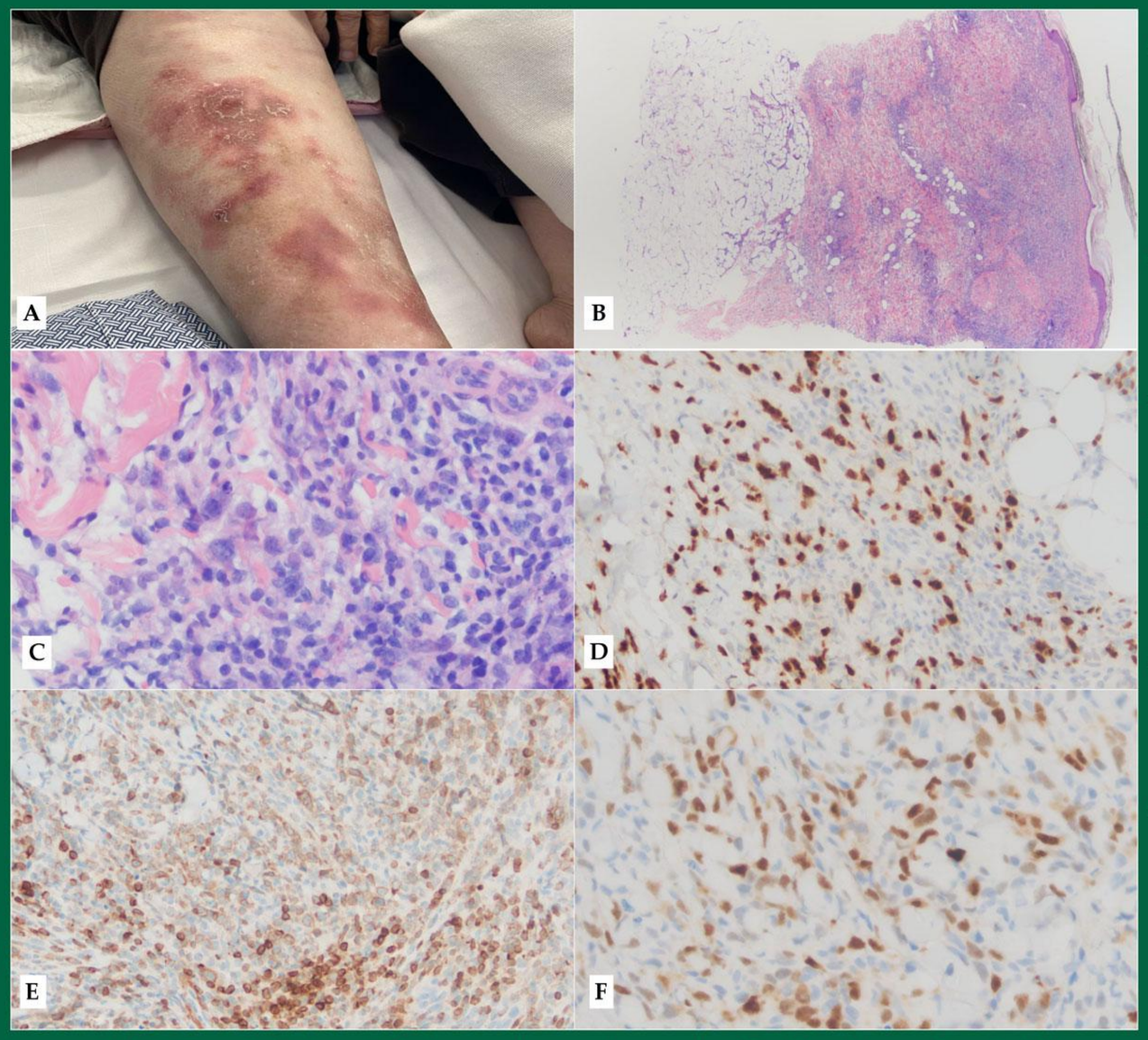

Image 1: (A) Exquisitely painful maculopapular rash affecting the entire right leg. (B) (20X, H&E) Punch biopsy of the maculopapular rash showing a pan dermal infiltrate of inflammatory cells. (C) (400X, H&E) Few large atypical lymphocytes admixed with small mature lymphocytes and histiocytes. (D) (400X, Pax-5 ICH) Pax-5 nuclear staining highlights the irregularity seen in the large atypical B-lymphocyte population. (E) (200X, BCL-2 IHC) Weak cytoplasmic staining of large atypical lymphocytes with strong expression in background small lymphocytes. (F) (400X, Mum-1 IHC) Strong nuclear expression Mum-1 in the large atypical lymphocytes. (E-F) This dual pattern of expression is commonly seen.

Treatment

- Cycle 1 of R-CVP (Rituximab, prednisone (100 mg daily), vincristine, and cyclophosphamide) started as an inpatient approximately 2 weeks after presentation due to patient frailty
- Rash and facial pain improved after first cycle of therapy, however patient still has some residual left facial nerve palsy
- Currently receiving cycle 2 of R-CVP

Discussion

- Primary cutaneous diffuse large B cell lymphoma, leg type usually presents in the elderly and posses a challenge in terms of treatment
- Anthracyclines based regimens are the standard of care however alternatives like R CVP are also acceptable
- Given high PDL-1 expression in these tumors another alternative is the combination of check point inhibitors with Rituximab that at least in one case publication had an excellent response with minimal side effects

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The authors have indicated that they have no conflicts of interest that relate to the content of this poster.

T cell/histiocyte rich B-cell lymphoma

T cell/ histiocyte rich B-cell lymphoma: A difficult diagnosis to make

Rachael Steinhauer[1], Olutayo A. Sogunro[2], Eugene Lewis[2]

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Background: Non Hodgkins Lymphoma (NHL) is among the top 10 causes of cancer mortality, and diffuse large B-cell lymphoma (DLBCL) is the most common type of NHL. Rarely, DLBCL appears with an atypical histologic presentation and an aggressive clinical course, termed T-cell/histiocyte rich B cell lymphoma (T/HRBCL). Because of its uncommon occurrence and varying presentation, the difficulty in T/HRBCL is in making the diagnosis.

Methods: Case: A 55-year-old male presented with acute on chronic renal failure, weight loss, and acute gastrointestinal bleeding. He was found to have significant retroperitoneal lymphadenopathy that was biopsied and revealed B-cell lymphoma. He rapidly declined, developing upper gastrointestinal bleed and septic shock. CT scan imaging of the abdomen revealed a large cystic mass lesion arising from the fundus of the stomach and infiltrating the spleen. He underwent an exploratory laparotomy, splenectomy, gastric wedge resection of the fundus, and a distal pancreatectomy. Pathology revealed T-cell rich B-cell lymphoma. He is being treated with R-CHOP therapy.

Results: A multidisciplinary approach is essential to obtain a definitive diagnosis for T/HRBCL. This patient presented initially with vague symptoms and had multiple re-admissions before a diagnosis was made. T/HRBCL is associated with an aggressive disease course and unclear evidence regarding adequate response to R-CHOP therapy, further underscoring the need for accurate diagnosis.

Conclusions: This case depicts the importance of understanding the varying clinical presentations, immunohistochemical analysis, and the diagnostic and therapeutic challenges of a patient with T-cell/histiocyte rich B-cell lymphoma.

T-cell/histiocyte Rich B-cell Lymphoma: A Difficult Diagnosis to Make

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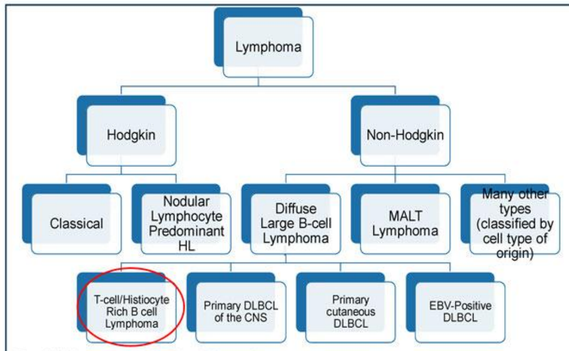
Abstract

Introduction: Non Hodgkin Lymphoma (NHL) is among the top 10 causes of cancer mortality, and diffuse large B-cell lymphoma (DLBCL) is the most common type of NHL.[1] Rarely, DLBCL appears with an atypical histologic presentation. Scattered malignant B cells on a background of T-cell and histiocyte-rich stroma define the diagnosis of T-cell/histiocyte rich large B cell lymphoma (T/HRBCL). Because of its uncommon occurrence and distinct presentation, the difficulty in T/HRBCL is in making the diagnosis.
Case: We present a case of a 55-year-old male who presented with acute on chronic renal failure, weight loss, and acute gastrointestinal bleeding. He was found to have significant retroperitoneal lymphadenopathy that was biopsied and revealed B-cell lymphoma. He rapidly declined, presenting with an upper gastrointestinal bleed and septic shock. CT scan imaging of the abdomen revealed a large cystic mass lesion arising from the fundus of the stomach and infiltrating the spleen. He was taken to the operating room for an exploratory laparotomy, splenectomy, gastric wedge resection of the fundus, and a distal pancreatectomy that found a gastric fundus perforation with erosion into the spleen causing a large splenic parenchymal abscess. Pathology revealed T-cell rich B-cell lymphoma. He is being treated with R-CHOP therapy.
Discussion: A multidisciplinary approach is essential to obtain a definitive diagnosis for T/HRBCL. This patient presented initially with vague symptoms and had multiple re-admissions before a diagnosis was made. T/HRBCL is associated with an aggressive disease course and unclear evidence regarding adequate response to R-CHOP therapy, further underscoring the need for accurate diagnosis.
Conclusion: This case depicts the importance of understanding the varying clinical presentations, immunohistochemical analysis, and the diagnostic and therapeutic challenges of a patient with T-cell/histiocyte rich large B-cell lymphoma

Introduction



T-cell/Histiocyte Rich B-cell Lymphoma

- Definition: fewer than ten percent malignant B-cells in the setting of polyclonal T cells with or without histiocytes.[2,3]
- Epidemiology: T/HRBCL accounts for only 1-3% of all DLBCL. T/HRBCL tends to present with a male predominance in a relatively young population with a mean age in the fourth decade of life.[2,4,5]
- Pathophysiology: repetitive antigenic stimulation of lymphoid tissue of the GI tract → monoclonal proliferation → lymphoma of a solid organ.[6]
- Distinguishing clinical features: high risk of bone marrow involvement, hepatosplenomegaly, aggressive clinical course, and high rates of extranodal malignancy.[2]
- Workup: radiographic and endoscopic evaluation including CT, MRI, EGD with biopsies with or without endoscopic ultrasound, and PET[7]
- Treatment: equivalent to the treatment of other DLBCL: R-CHOP chemotherapy regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone)[8]
  - T/HRBCL is very aggressive and some studies show inferior response to therapy.[9]

Timeline

Initial Presentation and Admission	Admission 2: ICU	Admission 3: ICU	Surgery	Pathology Reveals Diagnosis	Complica-tions	R-CHOP Therapy
Cc: Intermittent heartburn. Labs reveal anemia and azotemia	Cc: epigastric pain, coffee-ground emesis, hematochezia	Cc: septic shock	Exploratory laparotomy, splenectomy, gastric wedge resection of the fundus, distal pancreatectomy	T/HRBCL	Hypoxic respiratory failure and subacute left occipital stroke	Ongoing

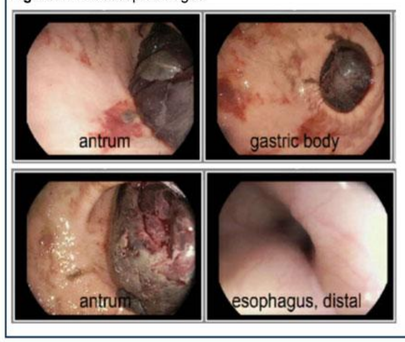
Case Description

Presentation:
55 y/o male with a PMHx of gout, CKD, and hypertension presents complaining of intermittent, severe burning in the back of the throat. He sought evaluation at an urgent care clinic where he was re-directed to the emergency department after his creatinine was found to be elevated. He had not been seen by a physician in over 10 years. He had an unintentionally 20 pound weight loss in the last three months.

Workup:
- anemia (hgb = 11g/dL, hct = 33.3%)
- azotemia (BUN = 63 mg/dL, Cr = 3.1 mg/dL)
- Moderate splenomegaly measuring 16.1cm with multiple hypoechoic masses within the spleen
- Multiple prominent retroperitoneal lymph nodes, largest measuring 4.8 x 4.5 x 4.4.
- CT-guided percutaneous biopsy of retroperitoneal lymph nodes: large B cell lymphoma with an intense population of T lymphocytes in the background (84% of lymphoid cells were T cells).

Readmission:
Chief complaint: Acute epigastric pain, coffee-ground emesis, hematochezia. Diagnosis: Gastric ulcers

Figure 1: Endoscopic images

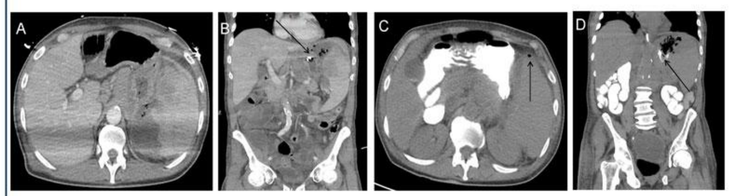


Endoscopic images of the stomach on the patient's repeat EGD in which a large clot formed in the antrum is visible. Superficial ulcers in the gastric body are also seen.

Gastric biopsy: lymphocytic infiltrate of the gastric mucosa with a mix of T- and B-lymphocytes, inconclusive for lymphoma. Negative for H. pylori.

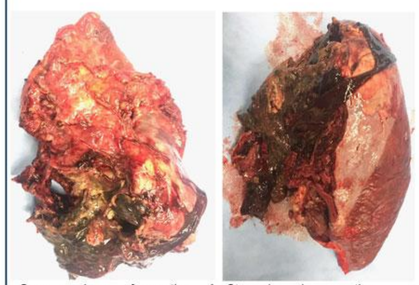
Readmission #2:
Chief Complaint: Syncope and GI Bleed. Diagnosis: Septic Shock from gastro-splenic abscess

Figure 2: CT scan images of the abdomen and pelvis



A. Axial image showing large heterogeneous predominantly cystic mass lesion arising from the fundus of the stomach **B**. Sagittal image showing a gastric cystic mass lesion with air lucencies within it, with surgical clips/staples noted at the base of the mass (arrow). **C**. Axial image depicting foci of extraluminal air at near superior pole of spleen (arrow). **D**. Sagittal image depicting large left subphrenic mass measuring abutting the stomach and spleen which extravasation of oral contrast into the cystic structure.

Figure 3: Gross specimens from surgical resection



Gross specimens of resection. A. Stomach wedge resection showing areas of necrosis and perforation. B. Spleen showing areas of infarct and distal tip of pancreas seen medially.

Operative Management: Exploratory laparotomy, splenectomy, gastric wedge resection of the fundus, distal pancreatectomy

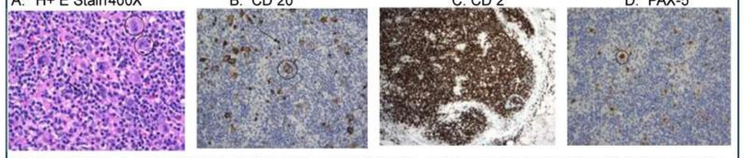
Findings: Gastric perforation with splenic parenchymal abscess.

Pathology of pancreatic node: T-cell/histiocyte rich B-cell lymphoma

A chemo port was placed for RCHOP therapy, and the patient was ultimately discharged home on hospital day 21.

Discussion

Figure 4: Histologic slides with immunohistochemical stains of the Pancreatic lymph node



Histological slides: **A**. High powered H + E stain showing abnormal B-cells. Encircled are giant malignant B-cells that can resemble Reed-Sternberg cells seen in Hodgkin Lymphoma. Arrow depicts multiple normal T cells in background. **B**. CD20 B cell marker; encircled are malignant B-cells. Arrow depicts normal B-cells. **C**. CD2 T-cell marker; brown cells are T cells staining in the majority. The islands of white are negative stains of the abnormal B-cells that are not stained. **D**. PAX5 B cell marker; stains the nucleus of the B cells. Encircled is the nucleus of a malignant B-cell.

- This case demonstrates the importance of a multidisciplinary approach to obtain a definitive diagnosis for T/HRBCL. In one study, the initial pathology of patients with T/HRBCL was incorrect in 82% of referred cases.[10]
- This patient's flow cytometry from the retroperitoneal lymph node biopsy showed abnormal morphology with 84% T-cells. The marked T-lymphocytic population in the background raised the possibility of T/HRBCL, but the number of large B cells appeared somewhat more than expected, so the diagnosis was not definitively made with the node biopsy.
- On pathology of the gross specimens, the spleen was infarcted with involvement of large B cell lymphoma with features consistent with T/HRBCL. The wedge resection of the gastric fundus had morphologically large abnormal neoplastic cells similar to the spleen but because they were infrequent, additional stains were not performed → if additional gastric tissue was resected, the lymphoma may have been detected.
- The definitive diagnosis came from evaluation of the pancreatic node present in the gross specimen. On hematoxylin and eosin (H + E) stains, abnormal B cells were clearly identified with multiple scattered T cells, **see Figure 4**.
- Cellular genetic profiling has revealed factors that may contribute to a tumor immune tolerance in the T/HRBCL microenvironment → may contribute to the aggressive nature of the disease. These immune factors may serve as a potential target for future therapy.[9]
- The patient's treatment plan is R-CHOP with high-dose methotrexate (HD MTX) in later cycles due to concerns for future CNS involvement.
- More research is required to investigate improved disease-specific treatments.[2] There is unclear evidence regarding whether there is a decreased response to R-CHOP in patients with T/HRBCL, but changes to the regimen have not yielded improvement.[8,11]

Conclusions

- This is an interesting case of a T-cell rich B-cell lymphoma in a 55-year-old male who presented late with stage 4 disease and solid organ involvement.
- Through the diagnostic and therapeutic involvement of multiple specialties, the appropriate diagnosis of T-cell/histiocyte rich large B cell lymphoma was ultimately made and the appropriate treatment with chemotherapy was initiated.
- This case depicts the importance of understanding the varying clinical presentations, immunohistochemical analysis, and the diagnostic and therapeutic challenges of a patient with T/HRBCL.

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Unusual presentations of high-grade B-cell lymphoma

Unusual presentations of high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements

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Background: High-grade B-cell lymphoma (HGBL) with *MYC* and *BCL2* and/or *BCL6* rearrangements is a clinically aggressive malignancy with frequent extranodal involvement and widespread disease at presentation. Approximately half transform from indolent lymphomas. Cytogenetic abnormalities define these entities, and timely submission of tissue for FISH is essential for proper diagnosis and treatment.

Methods: Case #1: 53-year-old man with knee pain and inguinal lymphadenopathy. Imaging revealed an irregular mass in the left popliteal fossa and widespread disease with osseous, soft tissue, and lymph node involvement. Biopsies showed inguinal marginal zone lymphoma and popliteal HGBL with *MYC* and *BCL2* rearrangements.

Case #2: 59-year-old woman with chest pain, dyspnea and leg swelling. Imaging revealed pleural effusions, pericardial effusion causing tamponade, pericardial mass encasing the RCA and compressing the right heart, and mediastinal lymphadenopathy. Pericardial fluid showed involvement by HGBL with *MYC* and *BCL6* rearrangements, and bone marrow biopsy showed low-grade follicular lymphoma.

Case #3: 65-year-old woman with chest pain, 10 cm mediastinal mass, diffuse adenopathy, leukocytosis, and thrombocytopenia. Flow cytometry of the peripheral blood revealed a CD10+ clonal B-cell population. Bone marrow biopsy showed involvement by HGBL with *MYC* and *BCL6* rearrangements.

Results: The 105 primary brain tumors consisted of 74 glioblastomas, 13 astrocytomas, 5 oligodendrogliomas, and 13 unspecified or other subtypes. 96/105 patients received successful GTT results. A total of 208 clinically actionable gene aberrations were listed in the successful reports. The most commonly mutated genes were, in order: EGFR, TP53, IDH1, PTEN, and CDKN2A. The average number of courses of treatment administered to each patient was 2.08; average duration of each course of treatment was 142.3 days. The most commonly prescribed drug was temozolomide, followed by bevacizumab, abemaciclib, trametinib, and pembrolizumab.

Discussion: We present three HGBL cases with unusual presentations: Two that transformed and involved uncommon extranodal sites, and one de-novo case with leukemic presentation. This series illustrates the wide spectrum of disease in HGBL. We emphasize that high suspicion and prompt cytogenetic identification are essential for accurate diagnosis and treatment.

UNUSUAL PRESENTATIONS OF HIGH-GRADE B-CELL LYMPHOMA WITH *MYC* AND *BCL2* AND/OR *BCL6* REARRANGEMENTS

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Background

High-grade B-cell lymphoma (HGBL) with *MYC* and *BCL2* and/or *BCL6* rearrangements is a clinically aggressive malignancy with frequent extranodal involvement and widespread disease at presentation. Approximately half transform from indolent lymphomas. Cytogenetic abnormalities define these entities and timely submission of tissue for FISH is essential for proper diagnosis and treatment.

Case 1

53-year-old man with knee pain and inguinal lymphadenopathy. Imaging revealed an irregular mass in the left popliteal fossa and widespread disease with osseous, soft tissue, and lymph node involvement. Biopsies showed inguinal marginal zone lymphoma and popliteal HGBL with *MYC* and *BCL2* rearrangements.

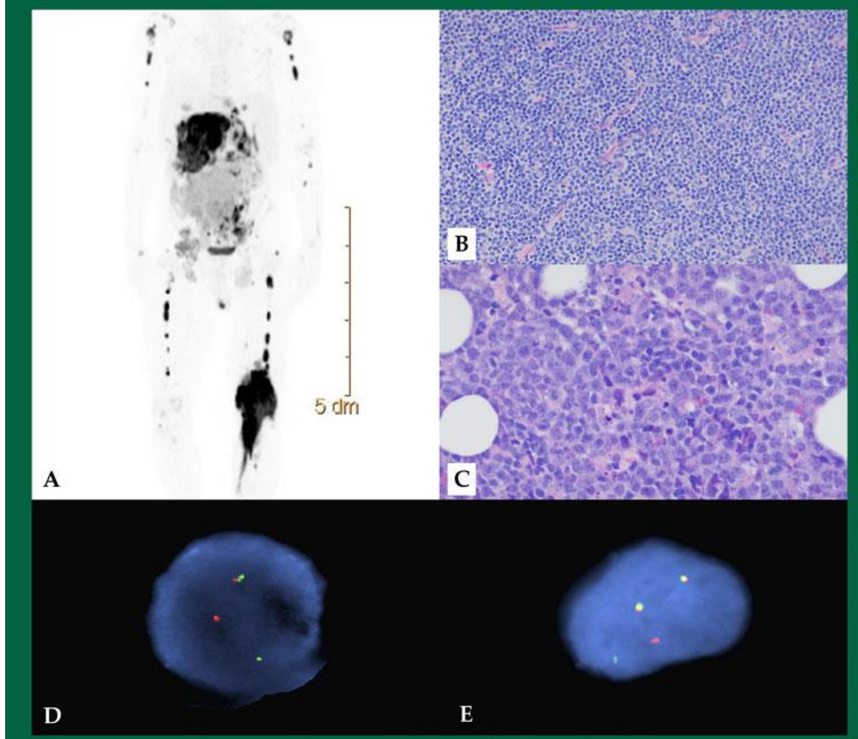

Figure 1: (A) PET scan shows a large popliteal mass with widespread involvement and inguinal adenopathy. (B) (200X, H&E) Inguinal node with sheets of small marginal zone lymphoma cells. (C) (400X, H&E) Popliteal mass with sheets of large irregular lymphoma cells infiltrating subcutaneous tissues. (D) (FISH) *MYC* 8q24.21 and (E) (FISH) *BCL2* 18q21.33-q22.1 breakapart probes showing abnormal patterns, indicating rearrangements.

References:
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Case 2

59-year-old woman with chest pain, dyspnea, pleural and pericardial effusions, pericardial mass encasing the RCA and compressing the heart, and mediastinal lymphadenopathy. Pericardial fluid showed involvement by HGBL with *MYC* and *BCL6* rearrangements, and bone marrow biopsy showed low-grade follicular lymphoma.

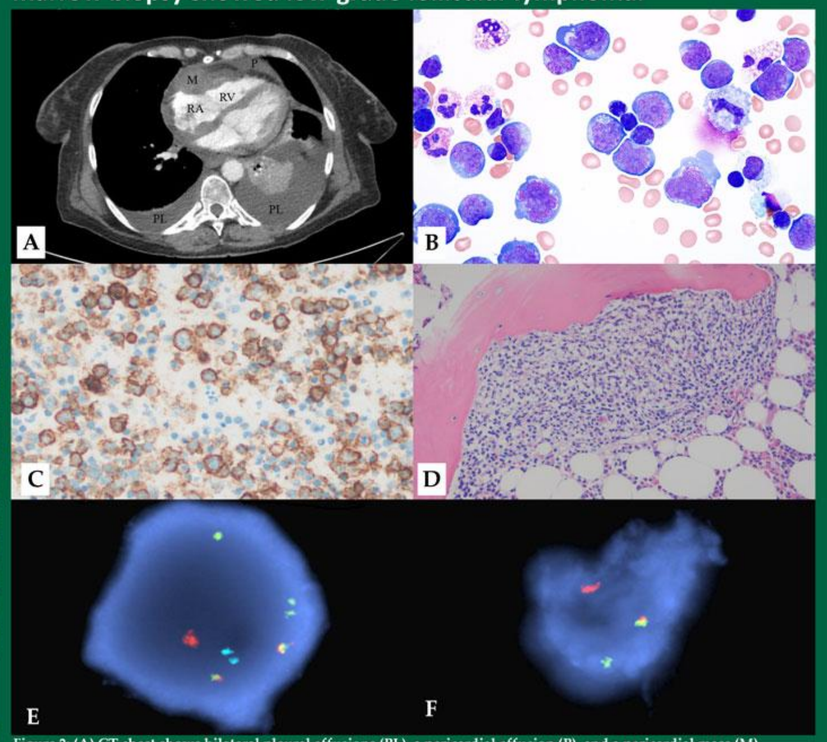

Figure 2: (A) CT chest shows bilateral pleural effusions (PL), a pericardial effusion (P), and a pericardial mass (M) compressing the heart (RA and RV) (image courtesy of Curtis Green MD). (B) (1000X, Wright Giemsa) pericardial fluid with large lymphoma cells. (C) (400X, CD20 IHC) Pericardial fluid cell block highlights large CD20 positive lymphoma cells. (D) (200X, H&E) Staging bone marrow biopsy with paratrabecular aggregate of small cleaved lymphocytes typical of follicular lymphoma. (E) (FISH) 8;14 dual fusion probe (*MYC*-8q24-Red CEP-8-Aqua 14q32-Green), with abnormal pattern indicating *MYC* alteration. (F) (FISH) *BCL6* q27.3-q28 breakapart probe with abnormal pattern indicating rearrangement.

Case 3

65-year-old woman with chest pain, 10 cm mediastinal mass, diffuse adenopathy, leukocytosis, and thrombocytopenia. Flow cytometry of the peripheral blood revealed a CD10+ clonal B-cell population. Bone marrow showed involvement by HGBL with *MYC* and *BCL6* rearrangements.

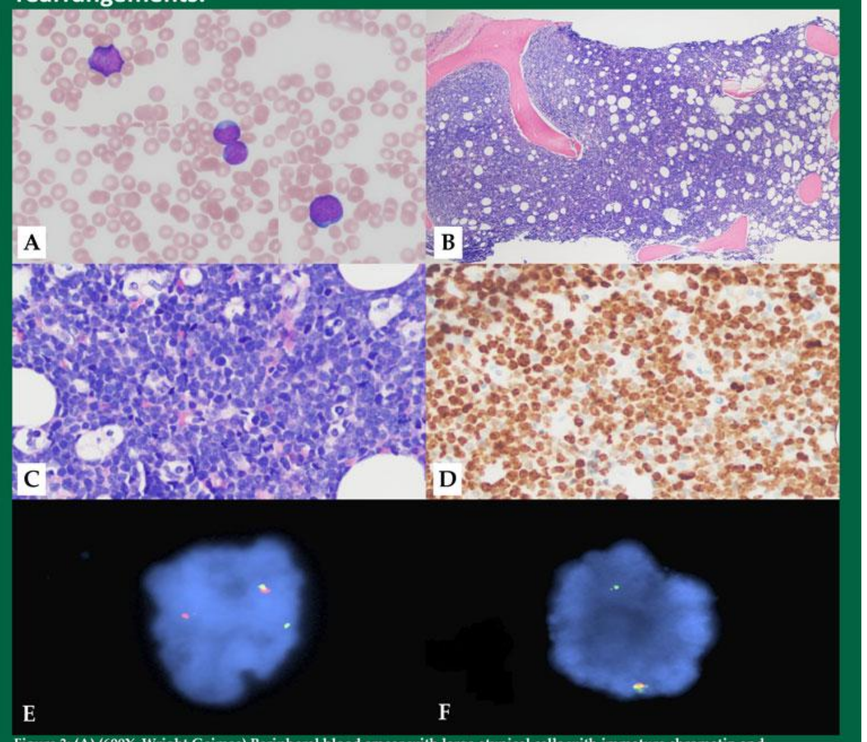

Figure 3: (A) (600X, Wright Geimsa) Peripheral blood smear with large atypical cells with immature chromatin and prominent nucleoli, consistent with circulating lymphoma cells. (B) (40X, H&E) Hypercellular bone marrow biopsy shows infiltration by lymphoma. (C) (400X, H&E) Large pleomorphic lymphoma cells. (D) (400X, Ki-67 IHC) Ki-67 shows strong nuclear staining in approximately 90% of lymphoma cells. (E) (FISH) *MYC* 8q24.21 and (F) (FISH) *BCL6* 3q27.3-q28 breakapart probes showing abnormal patterns, indicating rearrangements.

Discussion

HGBL with *MYC* and *BCL2* and/or *BCL6* rearrangements is a highly aggressive disease and is often advanced at diagnosis. We present 3 cases with quite unusual presentations: two that involved uncommon extranodal sites (popliteal fossa and pericardium), both of which were found to have transformed from low-grade lymphoma elsewhere; and one *de-novo* case with a leukemic presentation (blastoid phase). This series illustrates the wide spectrum of disease in HGBL with *MYC* and *BCL2* and/or *BCL6* rearrangements. We emphasize that a high index of suspicion and prompt cytogenetic evaluation are essential for accurate diagnosis, as these unusual presentations may mimic other hematologic malignancies or solid tumor on imaging and laboratory evaluation. Timely recognition guides upfront treatment for these patients as clinical outcomes with standard regimens for DLBCL are suboptimal.

The authors have indicated that they have no conflicts of interest that relate to the content of this poster.