AT THE FOREFRONT
UChicago Medicine

University of Chicago Department of Pathology
IRAP Case Presentations Handout
October 28th, 2019

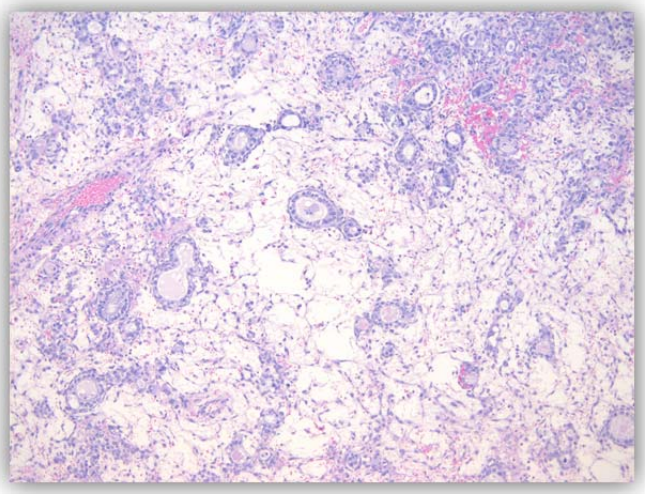
Case #1
Presenter: Kyle Kissick, MD
Attending: Jennifer Bennett, MD

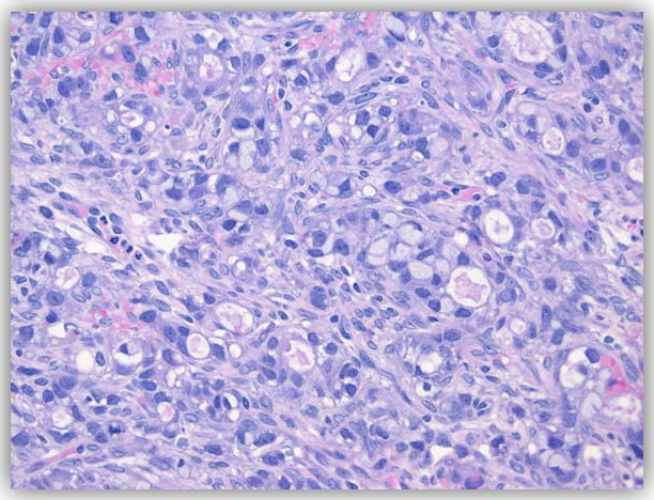
Clinical History
The patient is a previously healthy 20-year-old female who originally presented to an outside hospital for abdominal pain and distention with associated weight loss over a span of four weeks. She reported that her increasing abdominal girth led her to believe that she was pregnant, but multiple home pregnancy tests were negative. Her last menstrual period was reportedly four months prior to presentation. A pelvic ultrasound was subsequently performed and revealed an enlarged uterus with a "snowstorm appearance." Lab results at that time were unremarkable and her beta-HCG level was 2 mIU/mL. She was then transferred to the University of Chicago Medical Center with initial concern for a molar pregnancy. Further workup at UCMC with transvaginal ultrasound showed bilateral large solid and cystic ovarian masses with increased vascularity. CT abdomen and pelvis further characterized the bilateral masses as heterogeneously enhancing, with the right measuring 16.2 cm and the left measuring 13.4 cm in greatest dimension. Ascites and a large volume right pleural effusion were also noted on imaging. Pertinent laboratory values at the time of admission were as follows: CA-125: 332 U/mL (ref <35 U/mL), CEA: 8.1 ng/mL (ref 0-3.4 ng/mL), Ca 19-9: 5 U/mL (ref <37 U/mL), AFP: 24 ng/mL (ref <9.0 ng/mL). The Gynecologic Oncology service was consulted and the decision was made to proceed with exploratory laparotomy, bilateral salpingo-oophorectomy, omentectomy, and bilateral pelvic and para-aortic lymph node dissection.

Final Diagnosis
Metastatic adenocarcinoma with enteroblastic differentiation

Differential Diagnosis
- Yolk-sac tumor
- Sertoli-Leydig cell tumor
- Poorly differentiated carcinoma, gynecologic primary
- Adenocarcinoma ex goblet cell carcinoid, appendiceal primary
- Metastatic adenocarcinoma, unknown primary

Key Features
- Varying morphologies with areas of glandular differentiation and primitive intestine-like cells
- Hypocellular areas with a loose, reticular stroma
- Medium to large cells with hyperchromasia, nuclear variability, and clear to eosinophilic cytoplasm
- Patchy mucinous differentiation
- Presence of signet ring cells
- Abundant lymphovascular invasion





Discussion

Adenocarcinoma with enteroblastic differentiation is a rare, aggressive malignancy that is not well documented in the literature. Most accounts of this entity to date have been in the form of either single case reports or a small series of cases. The stomach is the most commonly affected organ, but there have also been reports of this malignancy arising in the esophagus, ampulla of Vater, and colon. Histologically, the tumor is characterized as having a primitive intestine-like structure composed of columnar or cuboidal cells with clear cytoplasm. Gastric adenocarcinomas with enteroblastic differentiation (GAED) have been shown to produce alpha fetoprotein (AFP) both in the serum and within the tumor itself. However, the precise association between GAEDs and AFP remains uncertain, as some tumors (such as in this case) may be AFP negative. In fact, up to 55% of GAEDs have negative staining for AFP according to one study. SALL4, which is a zinc finger transcription factor, has an essential role in maintaining the self-renewal and pluripotency of embryonic stem cells. Recent studies have demonstrated that this protein is also a specific marker not only in primitive germ cell tumors but also adenocarcinomas with fetal gut differentiation. Glypican 3, a cell surface heparan sulfate proteoglycan, is present in fetal liver and hepatocellular carcinoma or hepatoblastoma, and has also been proposed as a specific marker for enteroblastic differentiation. These two oncofetal proteins can, thus, be used in working up diagnostically challenging cases that exhibit a primitive cellular morphology resembling fetal gut. Furthermore, molecular studies on a small set of GAEDs have yielded information that might be useful in narrowing a differential diagnosis and excluding other entities. By far the most commonly mutated gene in GAED was found to be TP53, and most cases exhibited only the one pathogenic mutation. This would suggest that in the appropriate setting (i.e. SALL4 and glypican 3 positivity in a primitive appearing tumor) and with isolated TP53 mutations, a diagnosis of adenocarcinoma with enteroblastic differentiation should be highly considered despite its rare nature.

Learning Points

- Adenocarcinomas with enteroblastic differentiation are rare tumors that exhibit primitive intestine-like cells with columnar and cuboidal cells with clear cytoplasm
- SALL4 and glypican 3 are oncofetal proteins that serve as specific markers for enteroblastic differentiation; AFP is much less reliable and negative AFP staining does not preclude a diagnosis of adenocarcinoma with enteroblastic differentiation

The most commonly mutated gene in adenocarcinomas with enteroblastic differentiation has been found to be TP53, and these mutation frequently occur in isolation

Case #2

Presenter: Faiza Siddiqui, MD
Attending: Lindsay Alpert, MD

Clinical history:

A 58-year-old male presented to the emergency department with several days of vomiting and fever. He quickly became unresponsive and died shortly after presenting, presumably due to septic shock. Pre-mortem blood cultures grew predominantly *Lactobacillus* species. A complete autopsy was requested, which revealed a 5.0 cm area of induration in the gastric antrum resulting in gastric outlet obstruction, with copious amounts of partially digested gastric contents. Multiple white-tan nodules were also identified in the lungs, liver, omentum, small bowel, and colon.

Final diagnosis:

Lactobacillus sepsis secondary to probiotic use in a patient with widely metastatic gastric adenocarcinoma

Gross and Microscopic images:

Figure 1A:

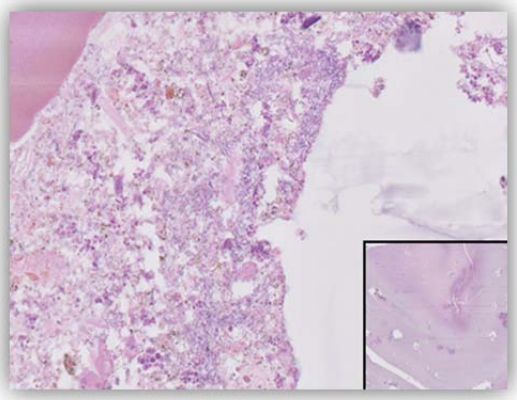


Figure 1B:

Figure 1. (A) H&E section of probiotic capsule with bacterial and fungal colonies (inset: intact portion of capsule). (B) Gross image of gastric contents with deflated capsules.

Figure 2A:

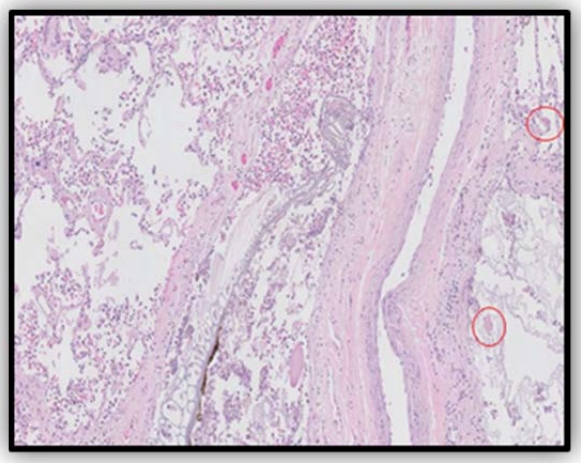


Figure 2B:

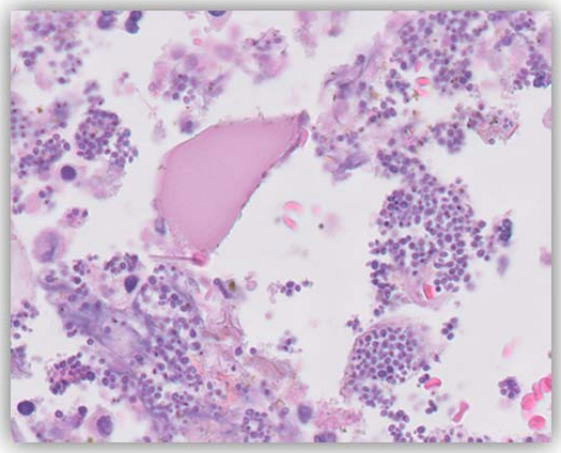


Figure 2. (A) Low power view of the lung with aspirated food and angulated eosinophilic capsule fragments. (B) High power view of capsule fragment with fungal and bacterial colonies.

Discussion:

Lactobacilli are Gram-positive, rod-shaped, facultative anaerobic bacteria. Their major function is to convert sugars to lactic acid. In humans, these organisms are normal commensals of the gastrointestinal and female genital tracts [1]. *Lactobacilli* are also one of the most common types of bacteria used in commercially available probiotics.

Probiotics are ingested mixtures of live microorganisms with a number of claimed health benefits, including maintenance of gut flora, improved immunity, prevention of urinary tract infections, lowering of body fat, and stress relief [2]. They are available in a variety of forms, including pills, syrups, dissolvable powders, and yogurts. Over the past two decades, the use of probiotics has increased dramatically. However, like other dietary supplements, probiotics are not FDA-regulated, and according to the European Food Safety Authority, there is no definitive scientific evidence to support many of their claimed health benefits [3].

Although the components of probiotics are generally considered to have low pathogenicity, invasive bacterial and fungal infections secondary to these agents have been reported. The literature on this topic is largely composed of individual case reports, along with a few case series and a review article. Cases of probiotic-associated sepsis were reported as early as the late 1970's, and over the past two decades, several cases of *Lactobacillus* bacteremia secondary to probiotic use have been published [4, 5,6,7,8,9].

Proposed risk factors for infectious complications of probiotic use include immunosuppressive conditions, prematurity, concurrent use of broad-spectrum antibiotics, disruption of the gastrointestinal barrier, presence of a central venous catheter, administration of probiotics by jejunostomy, use of probiotics with high mucosal adhesion or known pathogenicity, and cardiovascular disease [5,6,7]. According to the published literature, the majority of patients who developed complications following use of *Lactobacillus*-containing probiotics were immunocompromised, and malignancy was one of the common forms of immune compromise present in these patients. Indeed, in the autopsy case presented here, the patient had widely metastatic gastric adenocarcinoma, for which he was undergoing chemotherapy. He was reportedly ingesting multiple probiotic pills to ease the symptoms of gastric outlet obstruction. Both pre-mortem blood cultures and post-mortem lung cultures grew *Lactobacillus* species, a prominent component of the probiotics he was taking. The findings are consistent with a case of *Lactobacillus* sepsis secondary to probiotic use in a patient with malignancy- and chemotherapy-associated immune compromise.

In summary, although probiotics are generally considered safe and their use in healthy individuals should not necessarily be discouraged, probiotic-associated bacteremia can occur in patients with debilitating conditions or compromised immune systems. Therefore, caution should be taken when administering probiotics in patients with such conditions, including malignancies [8,9]. More research is warranted to further address the benefits and risks associated with probiotic use.

Learning points:

1. Probiotics contain proprietary mixtures of microorganisms that may have health benefits, but they lack FDA regulation.
2. Cases of invasive bacterial and fungal infections secondary to probiotic use have been reported in the literature, mostly in immunocompromised patients, including those with malignancies.
3. Common culprits in probiotic-mediated septicemia include *Saccharomyces* and *Lactobacillus* species.
4. Further research is needed to determine the prevalence of and risk factors associated with this phenomenon, as well as to prompt early recognition and allow for possible treatment.

Case #3

Presenter: Joseph Cho, MD, PhD
Attending: Peter Pytel, MD

Clinical History: The patient is a 14 year-old female without significant past medical history who presented with sudden, new onset tonic-clonic seizure. Initial CT imaging of the head revealed a 4 cm left temporal mass with subfalcine midline shift. Follow-up MRI demonstrated a heterogeneous mass arising within the left anterior, superior temporal lobe measuring (5.2 x 4.8 x 3.5 cm) containing recent internal hemorrhage. The lesion features subtle feathery internal enhancement (T1 after contrast shown in the included image). She suddenly deteriorated with acutely fixed and dilated left pupil. Repeat CT imaging revealed a new hemorrhage within the lesion and increased midline shift with uncal herniation. The patient underwent emergent craniotomy and mass resection.

Final Diagnosis: Glioblastoma multiforme (GBM), with histone 3 G34 mutation, WHO grade IV

Differential Diagnosis

- Other variants of glioblastoma multiforme (GBM)
- Diffuse midline glioma, H3 K27M-mutant (wrong anatomic location)
- Embryonal tumor "CNS-PNET"

Key Features

Variable tumor histology including:

- GBM-like areas with invasive, infiltrating high-grade tumor featuring satellitosis, palisading necrosis, brisk mitotic activity as well as more generic and pleomorphic areas with astrocytic features.
- Primative neuroectodermal tumor (PNET)-like regions with very primitive appearing cells featuring high N:C ratio and hyperchromatic, pleomorphic nuclei.

Immunohistochemistry findings:

- TP53 robustly increased
- ATRX negative
- IDH1 R132H negative

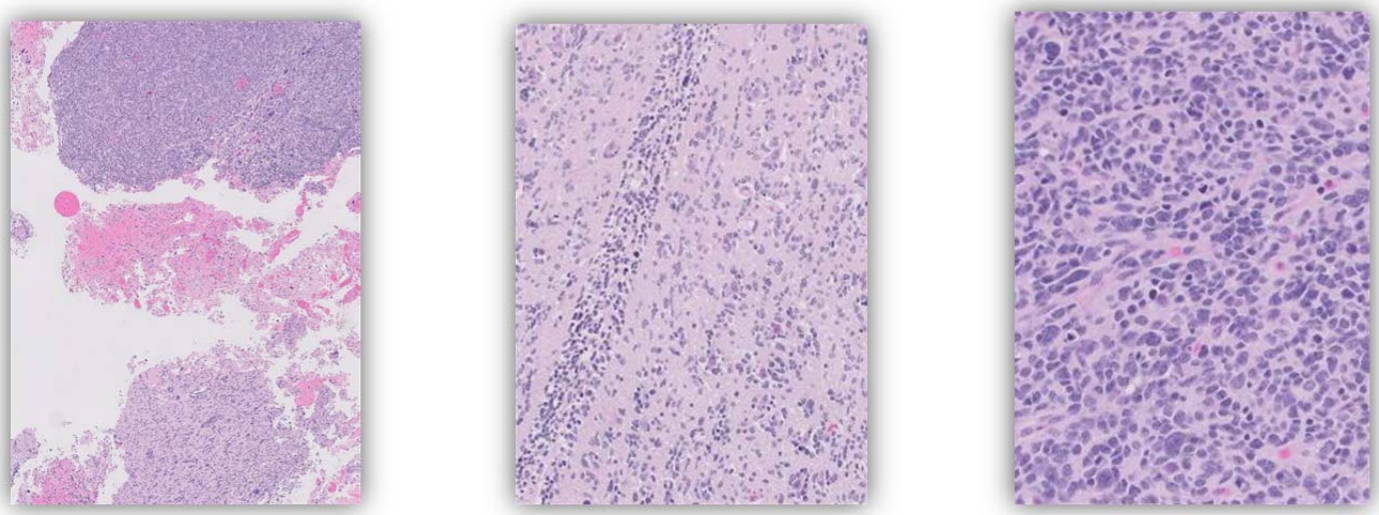
Clinical features:

- Hemispheric tumor location
- Age of patient: 14 years old

Key Molecular findings:

- ***H3F3A* c.103G>A, p.G34R**
- *ATRX* c.3145dup, p.I1049Nfs*4
- *TP53* c.526T>C, p.C176R
- No *IDH1* or *IDH2* mutations

A. **B.** **C.**



Figures. A. Tumor histology with PNET-like and GBM-like areas (2x). B. GBM-like area (10x). C. PNET-like area (20x).

Discussion

We present a hemispheric, central nervous system (CNS) tumor in a 14 year-old female featuring mixed GBM-like and PNET-like histology, *TP53* mutation, and *ATRX* loss. While in the past, this tumor would have been defined by morphologic features alone, the updated 2016 World Health Organization (WHO) classification of CNS tumors now integrates both genotypic and phenotypic characteristics in defining distinct tumor entities. Interesting, next generation sequencing (NGS) reveals a mutation in histone 3.3, H3F3A c.103G>A, p.G34R, in our patient's tumor which several studies suggest is the defining molecular feature of a distinct CNS tumor entity.

Tumors of the CNS with histone 3.3 G34 mutation (hereafter referred to as G34 mutants) vary in histopathologic appearance and include GBM-like, PNET-like or mixed histology. Despite the divergent histopathology, several lines of evidence including genetic, epigenetic, topographic, and epidemiologic features provide a compelling argument that G34 mutants represent a single nosologic entity. First, in addition to harboring histone 3 G34R/V mutations, over 90% of G34 mutants exhibit concurrent *TP53* mutation and *ATRX* loss. Additionally, about 70% of G34 mutants exhibit cytogenetic abnormalities with chromosomal loss of 3q or 4q. Compared to other recognized CNS tumor entities, G34 mutants also exhibit a distinct global DNA methylation pattern, suggesting that G34 mutants have a unique biological origin. Topologically, G34 mutants arise in the cerebral hemispheres, particularly the temporal and parietal lobes. In addition, the G34 mutants occur in younger patients with a median age of 18 years-old. Lastly, when G34 mutants are stratified by histology and analyzed for prognostic outcomes, there are no significant differences between GBM-like or PNET-like tumors, despite varying administered therapies. However, when G34 mutant tumors are stratified by oncogene amplification or *MGMT* promoter methylation status, prognostic differences are clearly appreciated highlighting the importance of genotypic features in these CNS tumors.

Histone 3.3 is a variant histone encoded by the gene *H3F3A*. Variant histone 3.3 is deposited in a cell-cycle-independent manner (unlike canonical histones such as histone 3.1 which are cell-cycle dependently expressed, assembled and deposited) and enriched at specific regions of the genome including highly transcribed genes, pericentric heterochromatin and at telomeres. Histones can be post-translationally modified at specific residues on their tail by methylation which in turn regulates gene transcription. While residue G34 on histone 3.3 is not modified by methylation, a residue in close proximity, K36 can be mono-, di- or tri-methylated. Mutations at G34 affect K36 methylation in *cis*, meaning only the K36 residue in proximity to the mutated G34 residue is directly affected. Mutated G34 disrupts the binding site for K36 dimethyl-specific methyltransferase and increases the affinity for lysine K36 trimethyl demethylase enzyme – both changes leading to aberrant K36 dimethylation. Interestingly, a recent study demonstrates that histone 3 K36 dimethyl

recruits DNA methyltransferase, DNMT3A, which may explain the distinct global DNA methylation pattern observed in G34 mutant CNS tumors.

Conclusion
In summary, we present a high-grade CNS tumor with a G34 mutation in histone 3.3 (*H3F3A* c.103G>A, p.G34R) which defines a unique CNS tumor entity. Key features associated with G34 mutant tumors include: divergent histopathology (GBM-like, PNET-like or mixed), *TP53* mutation and *ATRX* loss in the absence of IDH mutations, hemispheric tumor location, younger age of patient, and of course, molecular evidence of histone 3 G34 mutation.

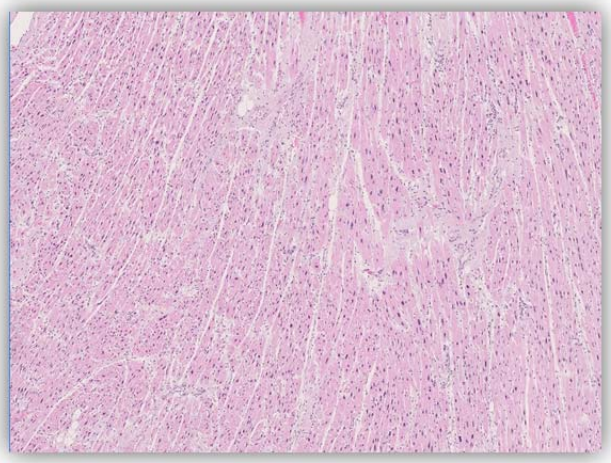
Case #4
Presenter: Maryam Asif, MD
Attending: Aliya Husain, MD

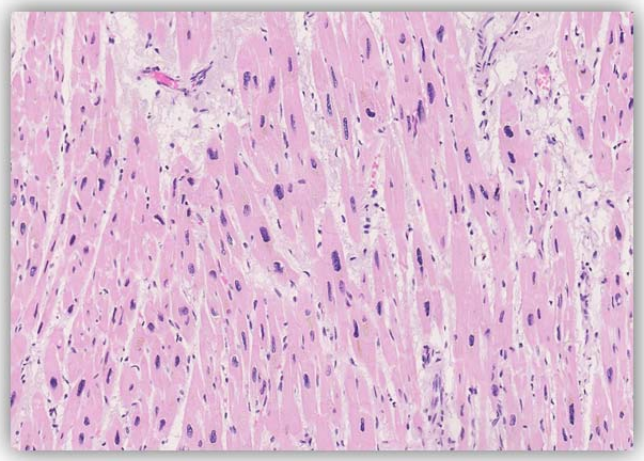
Clinical History
A 51-year-old female with a history of severe peripheral arterial disease status-post multiple amputations, type 2 diabetes, end-stage renal disease on hemodialysis, and cerebrovascular accident (2006) resulting in right side weakness. She was admitted to UCMC from an outside hospital with a gangrenous wound of the left hand and concern for underlying osteomyelitis. She was also hypotensive, with increasing lactic acidosis, concerning for sepsis. 2 days later she underwent amputation of the left hand but had continually worsening lactic acidosis with increasing pressor requirements, and developed unstable ventricular arrhythmias, which progressed to pulseless electrical activity and she expired 2 days after surgery. An autopsy was performed. Section of the heart is submitted for your review.

Final Diagnosis
Stress-induced (Takotsubo) cardiomyopathy

Differential Diagnosis
- Acute myocardial infarction
- Cardiomyopathies
    - Hypertrophic cardiomyopathy
    - Dilated cardiomyopathy
    - Restrictive cardiomyopathy
    - Catecholamine Cardiomyopathy

Key Features
- Myocyte hypertrophy with “boxcar” nuclei
- Interstitial fibrosis
- Scattered mononuclear infiltrates (no neutrophils)
- Contraction bands
- Grossly unremarkable heart with no evidence of hemorrhage, fibrosis, or infarct.
- The coronary arteries were patent





Radiologic features
A transthoracic echocardiogram (TTE) showed decreasing ejection fraction (from 60% to 35%).TTE compared to prior

study (from a day before) showed:

- Left ventricular performance moderately-severely reduced
- Significant left apical wall motion abnormality with akinesis of the left ventricular apical and mid-ventricular segments and hyperkinesis of the basal segments

Discussion

Stress-induced (Takotsubo) cardiomyopathy (TCM), is an acute and transient left ventricular wall-motion abnormality involving the apex and mid portions of the ventricle while sparing the base, which can simulate acute coronary syndrome in the absence of significant coronary artery stenosis. This cardiomyopathy was first described 1990 in Japan, and named after this bulging ventricle shape, that resembles a Takotsubo, a Japanese octopus fishing pot. Other terms for the disorder are: apical ballooning syndrome, broken heart syndrome, Neurogenic myocardial stunning.

Postmenopausal women are reported to make up over 90% of the cases in most series. Given that estrogen is a cardio protective hormone. It is thought that reduced estrogen levels after menopause can explain the predisposition of elderly women to Takotsubo cardiomyopathy. Exact prevalence of this disease is unknown, in United States 1-2% of the patients presenting with the clinical picture of myocardial infarction are ultimately diagnosed with Takotsubo. It seems, however, that these percentages underestimate the true prevalence of the disease, which in the thrombolysis era prior to primary angioplasty must have gone unnoticed on several occasions. It is often preceded by major emotional or physical stress.

Mayo Clinic has criteria for the diagnosis of Stress induced Takotsubo cardiomyopathy which includes:

- Transient akinesis or dyskinesis of the left ventricular apical and mid-ventricular segments w/ regional wall-motion abnormalities extending beyond a single epicardial vascular distribution
- Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture
- New ECG abnormalities (either ST-segment elevation or T-wave inversion)
- Absence of:
    - Pheochromocytoma
    - Myocarditis
    - Hypertrophic cardiomyopathy

Although the precise mechanism behind this contractile dysfunction remains elusive, it is thought to be due to a catecholamine excess resulting in microcirculatory dysfunction and direct myocardial toxicity combined with an abnormal response to increase in catecholamine such as epinephrine/norepinephrine. Studies have reported that there might be a mechanism to explain the apical ballooning and akinesia of apex that characterizes Takotsubo cardiomyopathy based on two overarching principles. Firstly, the apical-basal gradients of β-adrenergic receptors (βARs) in left ventricle, where apex contains the highest βAR and the lowest sympathetic nerve density leading to increased apical responsiveness to the catecholamines. Secondly, supraphysiological levels of epinephrine trigger β2-adrenoceptor to switch from Gs (stimulatory) to Gi (inhibitory) protein. This switch to Gi causes a negative inotropic response, thus contributing to the apical ballooning.

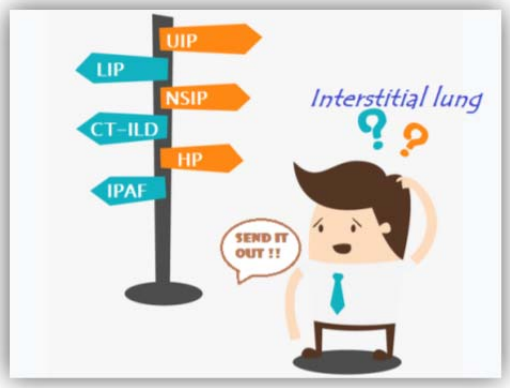
In this case, Takotsubo cardiomyopathy was preceded by significant physiologic stress (infection, septic shock, amputation). The patient's ECG findings were nonspecific, as is usual in 85% of TCM cases. The clinical and radiological features of TCM are well-documented, but the pathological findings are less so, as TCM is largely a clinical diagnosis. Described microscopic findings include myocyte hypertrophy, C4d positive myocyte necrosis, interstitial fibrosis, mononuclear cell infiltrate, and contraction bands with or without necrosis, the likes of which are present in the current case. Despite the generally good prognosis, complications of TCM include heart failure, thromboembolism, ventricular arrhythmia, and ventricular free wall rupture.

Learning Points

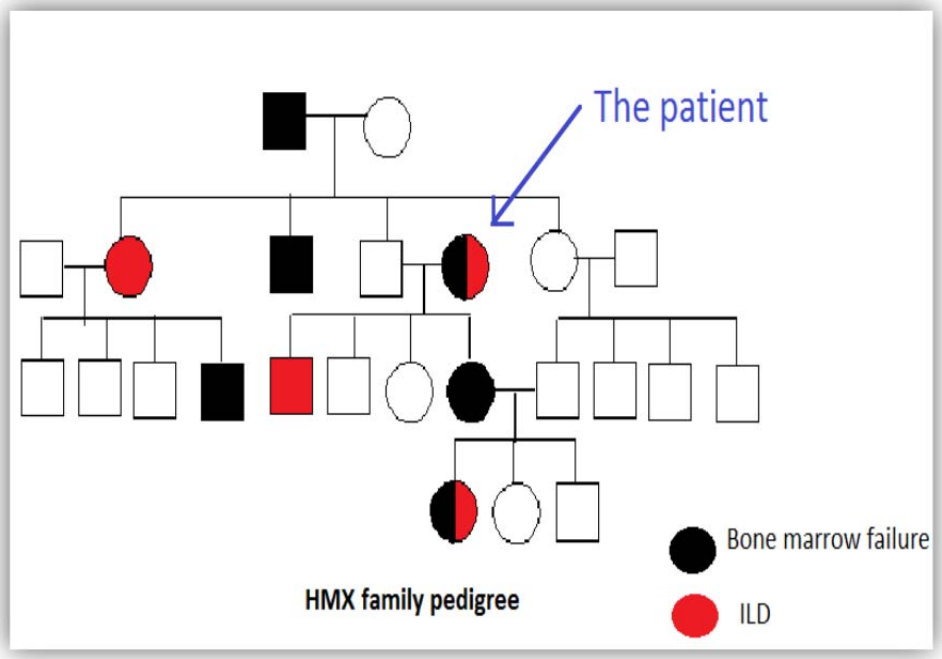
- Stress-induced (Takotsubo) cardiomyopathy should be considered a possible cause of sudden cardiac death resulting from arrhythmia or cardiac rupture in individuals without obvious heart disease.
- The duration of development TCM is short and range from 2 to 21 days.
- It is largely a clinical diagnosis, and a diagnosis of exclusion but the described histologic correlates along with the documented clinical and radiological features should guide in making the diagnosis

Case #5

Presenter: Urooba Nadeem, MD
Attending: Aliya Husain, MD



Clinical History
A 67-year-old male with a history of aplastic anemia that was unresponsive to treatment was being evaluated for bone marrow transplant. He presented with progressive shortness of breath and cough to his primary care physician. Initial treatment with steroids resulted in minimal improvement, but eventually, there was no response and the shortness of breath kept worsening. His care was transferred to the University of Chicago. Despite maximal medical management, the patient kept deteriorating and eventually progressed to respiratory failure and oxygen dependence. The patient underwent bilateral lung transplantation. **Multiple family members have a history of similar respiratory and bone marrow failure symptoms. Below is the pedigree chart (Figure 1).**



Final Diagnosis
Interstitial Lung Disease associated with Short Telomere Syndrome (STS)

Differential Diagnosis
1. Chronic hypersensitivity pneumonia (HP)
2. Idiopathic Pulmonary Fibrosis (IPF)/ Usual Interstitial Pneumonia (UIP)
3. Interstitial Pneumonia with Autoimmune Features (IPAF)
4. Connective Tissue Disease-associated interstitial lung disease (CTD-ILD)
5. Familial interstitial lung disease

Key Features
ILD with UIP pattern and unusual features:

1. Upper lobe predominance
2. Granulomata
3. Lymphoid aggregates
4. Lymphoplasmacytic infiltration
5. Pulmonary arterial hypertension

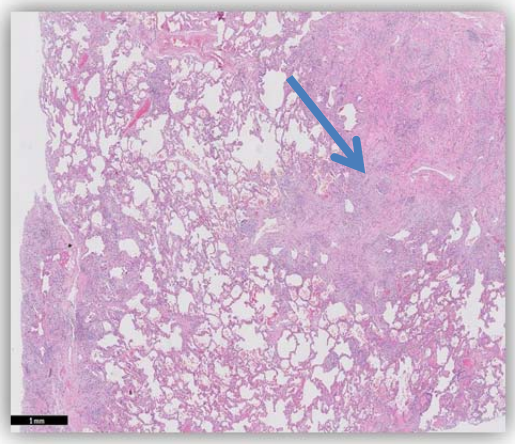


Figure2. Dense fibrosis (blue arrow)

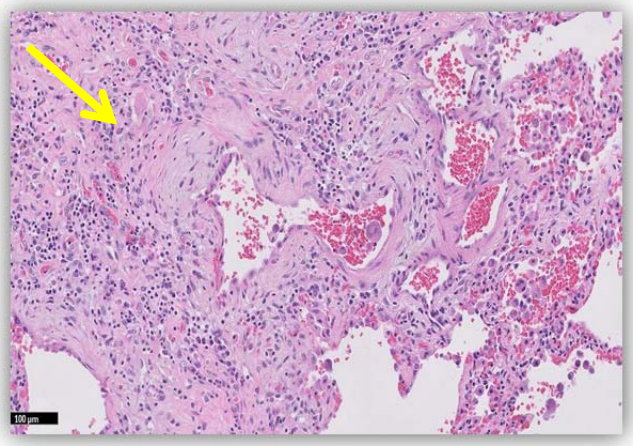


Figure3. Fibroblastic foci (yellow arrow)

Radiologic features

- Initial high resolution CT scan shows mild traction bronchiectasis in the sulcus and subpleural fibrosis
- The later scan shows advanced disease with severe honey combing, bronchiectasis and fibrosis

Additional testing

- <1% telomere length in both lymphocytes and granulocytes determined by flow FISH
- DNA sequencing shows TERT gene c.347 C>T.pThr116Ile

Discussion

Idiopathic pulmonary fibrosis (IPF) is a lethal disease that was until recently presumed to be a sequela of chronic inflammation; however, not all patients having a predisposing cause for chronic inflammation suffer from interstitial lung disease.[1]The treatment modalities that focused on reducing chronic inflammation failed in providing any benefit in these patients. A large number of studies have tried to pinpoint the genetic bases of this disease; however, even today a few studies with a sizeable number of patients are present. Familial IPF, which is indistinguishable from sporadic IPF, is defined as when two or more members of a family have the disease. [2] Some studies suggest that 0.5–3.7% of IPF is familial.[3,6] The most well-described causes are the mutations in surfactant production genes *SFTPA2*, *SFTPC*, and *ABCA3 and* telomere-associated genes such as *TERT*, *TERC*, *RTEL1*, *TINF2*, and *PARN.* [4,5,6]
Short telomere syndromes (STS) are a heterogeneous group of multisystem disorders characterized by decreased telomere lengths. [4] The accelerated decrease in length is usually due to inheritable gene mutations in the telomerase enzyme. Organs with high cell turnover, such as the bone marrow, lungs, gastrointestinal tract, and skin, are the most commonly affected.[4,6] Screening involves telomere lengths assessment in peripheral blood in both the granulocytes and lymphocytes and a confirmatory mutational analysis by next-generation sequencing to identify the specific mutation in the gene.[7]
We identified eight patients with short telomere syndromes through the registry for hematologic diseases at the University of Chicago. All these patients had the histologic findings of usual interstitial pneumonia (UIP) with unusual features not typically noted with the UIP pattern of disease; e.g. granulomata, upper lobe predominance, lymphoid aggregates, lymphoplasmacytic infiltration, and pulmonary arterial hypertension. It is imperative to identify this cohort of patients because they require different immunosuppressive regimens post-transplantation as they have a higher risk of myelosuppression (leukopenia and thrombocytopenia) and renal failure. [7,8]Also family members can benefit from the newly available antifibrotic drugs for treating early interstitial lung disease.

Learning Points

- "Idiopathic" pulmonary fibrosis (IPF) is becoming more well-defined entity as more genetic mutations are being described.
- If unusual findings are present histologically in a patient with suspected IPF/ UIP pattern a multidisciplinary approach with involving the genetic counsellors and additional familial testing is advised.

- Antifibrotics are now available for treatment that can be started very early in the course of treatment and are promising in reversing the disease process.

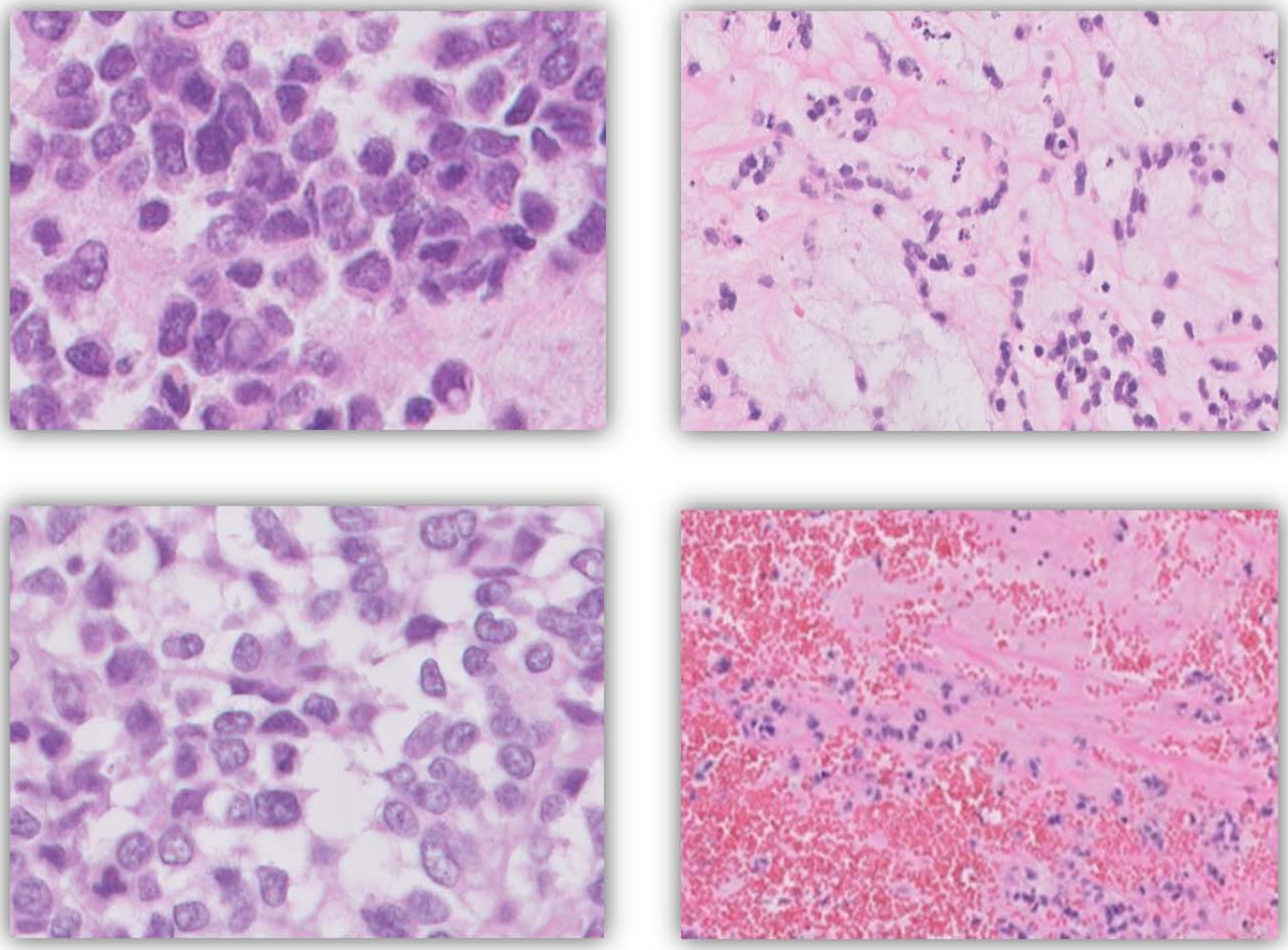
Case #6
Presenter: Luke Lauridsen, MD
Attending: Nicole Cipriani, MD

Clinical History
The patient is a 24-year-old male. He presented in 2011 to his primary care doctor for follow up of his medications and also noted a lump in his left upper extremity near the axilla. The lump was never painful and on palpation was mobile and thought to be cystic. Therefore, he was told it was most likely a benign cyst. In 2015 he noted that the lump was increasing in size so he sought medical attention. He was presented with a few options and elected to have the lump removed. The lump was 3.0 cm in size. An OSH diagnosis was made and positive margins were identified. A re-excision was performed and his case was discussed at an OSH tumor board. It was felt that his re-excision was curative and he did not undergo any adjuvant therapy. In early 2016 he had a surveillance MRI which was unremarkable. One year later (early 2017) he developed intermittent left chest discomfort and a CT was performed showing a 6.0 cm left lower lobe lung mass. He then underwent exploratory surgery with mass resection and left lower lobectomy. After pathology results (OSH) his case was discussed at tumor board again and he was started on adjuvant chemotherapy and followed. A few months later he presented to OSH ED with generalized tonic clonic seizure. An MRI was preformed which showed multiple bilateral cerebral metastases. Gamma knife was performed. He continued to be followed and had multiple OSH ED admissions for seizures. In late 2017 all of his pathology was received at UChicago and reviewed. At the end of 2017 he had another seizure and CT Head showed hemorrhagic metastases. He passed away two days later after transition to comfort care. A section of the lobectomy is submitted for your review.

Final Diagnosis
Undifferentiated Round Cell Sarcoma with CIC-DUX4 Translocation

Differential Diagnosis
- Synovial sarcoma
- Ewing sarcoma
- Undifferentiated round cell sarcoma with BCOR-CCNB3 translocation
- Undifferentiated round cell sarcoma with CIC-FOXO4 translocation
- Myoepithelial carcinoma
- Epithelioid MPNST
- Extraskeletal myxoid chondrosarcoma
- Malignant melanoma
- Merkel cell carcinoma

Key Features
- Geographic areas of hemorrhage and coagulative tumor necrosis
- Lobular architecture
- May be partially encapsulated
- Focal myxoid stromal matrix
- Moderate pleomorphic and coarse chromatin
- High mitotic rate
- Focal areas with cleared out cytoplasm due to glycogen accumulation
- Maybe areas of cells forming single file lines



Discussion

Undifferentiated Round Cell Sarcoma with CIC-DUX4 Translocation is a highly aggressive translocation-associated round cell sarcoma. It can present in a wide age range of patients with median age around 40 years old. As seen in this case, our patient was on the younger side. Due to its aggressive nature most patients will die within about two years as our patient did. Also, as demonstrated in our patient, this sarcoma has a high metastatic rate and, like synovial sarcoma, will most commonly metastasize to the lungs. Over the period of about 7 months our patient went from having no evidence of brain metastases to having seventeen with the largest 2.0 centimeters, further highlighting its aggressive nature. The extremities and trunk are the most common locations for this entity to arise but may arise in other locations including the brain.[1,2] Like most small round blue cell tumors the differential diagnoses is quite large.

When presented with such a case one may consider the following in one's differential diagnosis, extraskeletal Ewing sarcoma, poorly differentiated synovial sarcoma, alveolar rhabdomyosarcoma, epithelioid malignant peripheral nerve sheath tumor, myoepithelial carcinoma, Merkel cell carcinoma, melanoma, extraskeletal myxoid chondrosarcoma, and other undifferentiated round cell sarcomas, such as CIC-FOXO4 and BCOR-CCNB3. While ultimately cytogenics or PCR will need to be performed to clinch the diagnosis, unless DUX4 IHC is available, there are some histological clues to narrow down the differential diagnosis.[2]

Some histologic clues to the diagnosis, while nonspecific are still helpful. One should be on the lookout for areas of geographic necrosis, lobular architecture, possible a capsule or partial capsule, areas of myxoid stroma, moderate pleomorphism, clear to eosinophilic cytoplasm, high mitotic rate, perhaps areas of tumor cells forming single-file lines. Many of the histologic features will overlap with Ewing sarcoma and other sarcomas, such as areas containing small round blue cells with cleared cytoplasm due to glycogen accumulation. To further narrow down the diagnosis one should look for areas of desmoplasia which would suggest DRSCT or the CIC-FOXO4 translocation sarcoma.[4] While a mixed population of round cell and spindled cell would be more suggestive of the BCOR-CCNB3 translocation sarcoma.[5]

Learning Points

- When Ewing sarcoma is on your differential and CD99 is focal one should think of these Ewing-like translocation entities
- CIC-DUX4 can be detected with IHC
- CIC-FOXO4 sarcoma should show desmoplastic stroma
- BCOR-CCNB3 sarcoma should show mixed round cell and spindled areas

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