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Proceed With Caution: Drug Interaction Complicates Use of Nirmatrelvir/Ritonavir in Kidney Transplant Recipients With COVID-19

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A Rare Case of Pleomorphic Fibroma Associated with Li-Fraumeni Syndrome
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**Mentor:** Dominick DiMaio

**Program:** Pathology

**Type:** Case Report

**Background:** Li-Fraumeni syndrome is a germline mutation in the TP53 gene which causes an increased risk of various neoplasms like ovarian, colorectal, soft tissue, and hematopoietic tumors. Recently it has been associated with pleomorphic fibroma (PF), a rare benign dermal entity that clinically resembles other pedunculated/papillomatous lesions.

**Case:** We present a case of a 49-year-old Caucasian female with a past medical history significant for Li-Fraumeni syndrome, cutaneous leiomyosarcoma, and lung adenocarcinoma. She presented to her dermatologist with a 0.8 cm, soft mass in the left superior back. Clinically, the differential was broad and included lipoma, sarcoma, and desmoplastic melanoma, warranting an 8 mm punch biopsy. The biopsy demonstrated a mildly cellular proliferation of loosely arranged spindle cells with occasional prominent cytologic atypia (Figure 1A & 1B). No mitosis or necrosis was identified.

Histologically, the differential includes giant cell fibroblastoma, dermatofibroma with monster cells, sclerotic fibroma, pleomorphic lipoma, and pleomorphic liposarcoma. Immunohistochemical staining for CD34 (Figure 1C) and p16 (Figure 1D) was diffusely positive, with no significant staining for smooth muscle actin, desmin, or SOX10.

**Conclusion:** Li-Fraumeni syndrome is a germline mutation in TP53 which plays a crucial role as a tumor suppressor. When mutated, the role is disrupted. PF is linked with loss or deletion of chromosomes.

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Invasive Gastrointestinal Mucormycosis in Inflammatory Bowel Disease
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**Mentor:** Mark Kusek

**Program:** Pediatrics

**Type:** Case Report

**Background:** Mucormycosis is an often fatal, angioinvasive fungal infection mostly affecting immunocompromised patients. Timely diagnosis is challenging as symptoms of gastrointestinal mucormycosis (GIM) are non-specific. Features include: grossly, black necrotic bowel; endoscopically, necrotic ulcerations or ischemic changes; and microscopically, invasion of blood vessel walls, thrombi, and tissue infarction. Proper treatment comprises surgical debridement, antifungals, and immunosuppression reduction.

**Case:** A 15-year-old female newly diagnosed with Crohn’s Disease on 6-mercaptopurine, prednisolone, and infliximab suffered a disease course complicated by unremitting abdominal pain, enterocoleonic fistula and ileal narrowing, and resection of an obstructed, dilated small bowel segment. On post-operative day 6 from resection, she developed acute abdominal pain with fever. X-ray showed pneumatosis intestinalis with possible bowel ischemia. CT scan revealed intra-abdominal free fluid and possible free air (Figure 1). Surgery uncovered frank small bowel necrosis likely secondary to a thrombus and murky pelvic fluid suggesting microperforation. The necrotic bowel was resected. Fluid fungal cultures resulted positive for Mucor indicus. Amphotericin B was initiated, biologic and immunomodulators were held, and steroids weaned off. Repeat endoscopy 8 weeks later showed minimal sigmoid colitis. The patient completed 12 weeks of amphotericin B prior to resuming IBD management.

**Conclusion:** The defective immunity in IBD compounded with immunosuppressive drugs increases the risk of invasive fungal infections. With significant abdominal pain since Crohn’s Disease onset, it is tough to ascertain when this patient’s GIM developed. Of interest, despite pausing her IBD treatment, by treating her mucormycosis, the patient’s Crohn’s activity improved considerably on repeat endoscopy with near resolution of her once debilitating pain.

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Figure 1. Abdominal x-ray (left) showing severely dilated bowel loops and pneumatosis intestinalis in the left quadrants and pelvis. Sagittal view of abdominal CT scan (right) showing free intra peritoneal air and fluid, dilated bowel loops, and signs of peritonitis.
13q and 17p; the loci for retinoblastoma (RB) and TP53, respectively. The loss of heterozygosity cause tumorigenesis through downstream transcriptional dysregulation and increased genomic instability. One must have a heightened suspicion of germline TP53 mutation in patients presenting with multiple PF with a recommendation for further workup.

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Figure 1: There is mildly cellular proliferation of loosely arranged spindle cells, some of which have prominent cytologic atypia (A&B). No mitosis or necrosis was identified. The atypical cells stain positive for CD34 (C) and p16 (D)

Cutaneous Findings as a Harbinger for a Disseminated Fungal Infection
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Mentor: Corey Georgesen
Program: Dermatology
Type: Case Report
Background: Histoplasmosis is a systemic infection caused by the dimorphic fungus Histoplasma capsulatum. The fungus is often found in the Ohio River Valley and tropical countries. Frequently, the disease is asymptomatic or presents with self-limited pulmonary involvement. Rarely, it may present as disseminated disease in immunocompromised individuals.

Case: A 62-year-old immunocompromised male with end-stage renal disease secondary to lupus nephritis was admitted for altered mental status. Upon examination, the patient had pink umbilicated and ulcerated plaques in the left alar facial groove and on the left cheek present for three months. The patient endorsed hemorrhagic discharge and enlargement of both lesions for one month along with daily fevers. The patient traveled frequently to Central America. A punch biopsy of the left cheek revealed granulomatous inflammation with multinucleated giant cells containing intracellular organisms. GMS stain was positive for fungal yeast organisms with capsules. Lumbar puncture showed an elevated white count, low glucose, high protein, and elevated opening pressure. Histoplasma antigen was positive in the cerebrospinal fluid and serum. Interestingly, urine histoplasma antigen was negative. The patient was diagnosed with disseminated histoplasmosis and histoplasma meningitis and treated with intravenous liposomal amphotericin B for 6 weeks. At follow-up, he demonstrated significant improvement and was transitioned to oral itraconazole for at least one year.

Conclusion: This case likely represents a case of primary cutaneous infection given the longstanding nature of the patient’s skin lesions prior to systemic symptoms. Cutaneous manifestations of disseminated histoplasmosis are variable and nonspecific but may aid in diagnosis of the disease.

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Unexplained RV Lead Failure Manifesting as Atonic Seizures
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Mentor: J. William Schleifer
Program: Internal Medicine
Type: Case Report

Background: Pacemaker lead failure is a rare, but significant complication which can present in many ways. We present a case of pacemaker lead failure misdiagnosed as atonic seizures.

Case: A 38-year-old male with a past medical history significant for Down’s Syndrome, VSD status post patch repair, complete heart block status post dual chamber pacemaker placement presented with 4 months of recurrent seizure-like activity. Pacemaker interrogations revealed no significant arrhythmia and normal parameters. Multiple EEGs failed to capture any seizure-like activity. Prior to discharge, the patient had a seizure-like episode and became markedly bradycardic. Repeat EEG showed bradycardia followed by a syncopal episode with non-epileptiform shaking. ECG showed complete heart block, while telemetry review revealed complete heart block followed by failure to capture (Figure 1). Pacemaker interrogation after the event was unremarkable.

We determined the etiology of the patient’s seizure-like activity to be secondary to RV lead failure. Lead exchange was performed. Anti-epileptic medications were stopped, and no further episodes of seizure-like activity or complete heart block recurred.

Conclusion: Pacemaker lead failure should not be counted out in patients with recurrent seizure-like events, even after normal pacemaker interrogations. This case highlights the importance of considering lead failure in a patient presenting with recurrent seizure-like activity with no known source.

Proceed With Caution: Drug Interaction Complicates Use of Nirmatrelvir/Ritonavir in Kidney Transplant Recipients With COVID-19
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Mentors: Scott Westphal, Clifford Miles
Program: Nephrology
Type: Case Report

Background: Kidney transplant recipients are at increased risk of severe COVID-19 infection due to immunosuppression and poor vaccination response. Antiviral therapies are important to mitigate risk of severe disease. Nirmatrelvir/ritonavir, an oral antiviral, has been used in higher risk patients with COVID-19. Unique to transplant patients is the risk of calcineurin inhibitor (CNI) drug interaction and toxicity.

Case: A 57-year-old male received a kidney transplant 8 months ago. Immunosuppression includes tacrolimus, mycophenolate, and prednisone. He was fully vaccinated and boosted against SARS-CoV-2. He presented with fevers and body aches, and COVID test was positive. His primary care provider prescribed nirmatrelvir/ritonavir, and immunosuppression was continued. Two days later he developed vomiting and diarrhea prompting emergency evaluation.

Nirmatrelvir/ritonavir was continued, and tacrolimus was held. Two days later, tacrolimus level was checked and resulted at 75.6 ng/mL, complicated by acute kidney injury. He was admitted, treated with fluids and phenytoin to enhance CNI metabolism. Graft function improved, and tacrolimus level decreased but remained high (54 ng/mL). Tacrolimus remained on hold at discharge and was restarted when level normalized.

Conclusion: Nirmatrelvir inhibits Mpro, a protease enzyme required for SARS-CoV-2 replication. As a potent inhibitor of CYP3A, nirmatrelvir/ritonavir may interact with drugs metabolized through this pathway, including CNIs. Use of nirmatrelvir/ritonavir with CNIs requires extreme caution. The antiviral benefit may be opposed by risks incurred through drug interaction. If used, we recommend holding or reducing the CNI dose and close monitoring of levels. Providers and patients should be educated about this interaction, and alternative treatments may be preferable.

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Importance of Following Up on a PSA
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Mentor: Sarah Howard
Program: Clarkson Family Medicine
Type: Case Report

Case: Patient is 69-year-old male who has for the past 20 years had his PSA checked annually. He had many years history of urinary frequency and nighttime awakening that was attributed to benign prostatic hyperplasia (BPH). Every year he had a normal PSA for his age but from last year’s PSA to this year’s his level increased by 0.8. Based on his PSA level’s velocity the decision was made for him to see urology. With urology the decision was made to order a magnetic resonance imaging (MRI) which showed a prostate without abnormal lesions (recommended for a year follow up). Though the patient’s MRI was without lesions his PSA was too elevated for the size of his prostate, so a biopsy was performed. The pathology came back with prostate cancer (Gleason Score 9) and patient later went on to have a radical prostatectomy.

Conclusion: This patient’s case shows the importance of having an informed discussion with males about screening for prostate cancer. It also shows the importance of looking at a trend in PSA results to know when it is the time to refer to urology for further workup.

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A Case of Severe Cervical Dystonia After Radiofrequency Ablation
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Mentor: Amy Hellman
Program: Neurological Sciences
Type: Case Report

Background: Cervical Dystonia that has exhausted all treatment options sometimes is treated with Radiofrequency Ablation (RFA). In this case, the patient developed severe cervical dystonia two days post RFA ramectomy for an alternate diagnosis of refractory neck and arm pain. Case: A 56-year-old female presented with severe cervical dystonia and pain following RFA at levels C2 through C5 for untreatable left arm pain. Of note, with a history of mood disorder she was on brexpiprazole at the time of surgery, but this was a stable medication that had not had any adjustment in the last two years. Her dystonia had no improvement with removal of the antipsychotic nor other dystonia treatments, other than trihexyphenidyl.

Conclusion: We believe the etiology of her dystonia to be due to peripheral nerve injury from the RFA procedure, as acute dystonic reaction, tardive dyskinesia/dystonia, and functional dystonia were ruled out due to stability of her medications, persistence of symptoms, severe degree of hypertrophy, and lack of distractibility.

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Successful Use of Plasma Exchange Preceding RBC Exchange in Sickle Cell Disease Hyperhemolytic Crisis with Hepatic Sequestration: A Case Report
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Mentor: Oleg Bobr
Program: Pathology
Type: Case Report

Background: Hyperhemolytic crisis is an uncommon complication of Sickle Cell Disease (SCD) that may cause multiorgan failure and lead to significant mortality with no current national or international guidelines. We are presenting a case where hyperhemolytic crisis was complicated by hepatic sequestration and acute liver failure, that was dramatically reversed by 2 plasma exchange treatments followed by RBC exchange.

Case: A 35-year-old African American male with SCD and beta thalassemia trait presented with pain and was admitted for intravenous hydration and pain control. Laboratory work showed bicytopenia with a drop in hemoglobin (Hb) from 10.5 to 5.8 g/dL and platelets from 100 to 22 X10E3/uL. Various laboratory markers were abnormal including: Lactate dehydrogenase (LDH: 434 to 2848), creatinine, and blood urea nitrogen. Disseminated intravascular coagulation and Heparin-induced Thrombocytopenia antibody panel were negative. Abdominal ultrasound demonstrated mild splenomegaly. The clinical presentation and hepatocellular pattern of injury was consistent with hepatic sequestration crisis. Apheresis services were consulted after receiving blood products (1 unit of platelet and 3 units of pRBC). Plasma exchange was initiated for 2 procedures on consecutive days followed by RBC exchange with rapid improvement in clinical status and laboratory findings.

Conclusion: It is hypothesized that the hemolysis leads to release of free Hb and free heme that activate neutrophils, and vascular endothelial cells via TLR-4. This ultimately leads to decreased nitric oxide bioavailability which further contributes to SCD complications such as pulmonary and systemic vasculopathy. This provides a rationale for plasma exchange - removal of free heme from the patient plasma.

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