CLINICAL VIGNETTE

Erdheim Chester Disease – Two Cases of a Rare Disorder

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A 55-year-old female presented to hematology in 2015 with anemia, leukocytosis and thrombocytosis. She had prior pituitary adenoma surgery and Diabetes Insipidus, and pan hypopituitarism with central hypothyroidism on replacement therapy. Brain MRI in 2014 showed nodular enhancement in pituitary fossa. She also had significant chronic otitis externa.

In 2013, two years before she had persistent left upper abdomen pain, with CT abdomen which showed infiltration of omental fat and peritoneal thickening and stranding, with biopsy showing chronic inflammation. MRI abdomen one year prior showed soft tissue thickening and enhancement around abdominal aorta at origin of renal arteries, extending to the aortic bifurcation which had increased with soft tissue retroperitoneal and omental thickening compared with prior scan.

She had cholecystectomy and omental biopsy showing "inflammation". She underwent colonoscopy with polyps removal from transverse colon. Multiple colon mucosal biopsies showed infiltration with neoplastic epitheloid cells positive for vimentin, CD68, CD163, CD1a and focally positive for S100 and negative for CD34 and CAM 5.2. Biopsy was read as consistent with Langerhans Histiocytosis. Subsequent omental and pelvic and hepatic peritoneal nodules biopsies in 2016 described focal CD1a negative histiocytes and multi lobated giant cells but was read as reactive inflammation and fibrosis.

Positron emission tomography scan showed moderate FDG uptake with omental and retroperitoneal thickening and nodularity. There was also bilateral joint uptake and some marrow uptake in limbs.

She had recently developed renal insufficiency which improved after placement of bilateral renal artery stents. Renal function deteriorated with bilateral proximal ureteral narrowing which improved with placement of bilateral ureteral stents.

Follow-up PET scan in 2018 showed increased thickening, haziness and stranding and increased metabolic activity of SUV of 6.5 in the retro peritoneum, peritoneum and omentum (with nodules) and around major thoracic vessels and pericardium and pleura with some effusions. There was a new sclerotic T11 lesion but without increased metabolism.

In September 2018 she underwent laparoscopic omentectomy and peritoneal biopsies showing extensive infiltration with atypical histiocyties with spindled to epitheloid cells with faint eosinophilic cytoplasm with some vacuolation with multinucleated giant cells (tuton cell like) per one pathologist review. There was mild to focally moderate inflammatory cells and some mesothelial hyperplasia. These cells showed positivity to vimentin, CD68 and S100 and CD168 and Factor X111a. C1a was initially reported negative but on repeat testing reported positive. BRAF was negative on molecular staining but diagnosis of Erdheim Chester Disease was favored. Molecular studies showed clonal MAP2K1 and RUNX 1(NTP18-019767) mutations and diagnosis was changed to consistent with ECD.

She developed worsening renal function with biopsy showing acute tubular necrosis (ATN). Her ATN was attributed to polyuria and dehydration despite chronic intravenous hydration and DDAVP.

Echo in late 2018 was normal but in early 2019 showed moderate pericardial and mild pleural effusions and mild sclerosis and regurgitation of aortic and mitral valves. She complained of sweats, low grade fevers and some respiratory symptoms over time. Beside leukocytosis, thrombocytosis and anemia she had elevation of CRP and sedimentation rate.

She started Cladribine before complete molecular testing but stopped after 3 doses because of worsening renal insufficiency. Once the MAPK pathway mutation was confirmed she was switched to MEK inhibitor Cobimetnib.

A second patient is 77-year-old male who underwent right hemicolectomy for adenocarcinoma in situ with negative nodal sampling. At the time of surgery his liver was noted to be atypical in appearance and liver biopsy and sampling of one mesenteric node found a small T cell population without convincing evidence of lymphoma. MRI abdomen showed massive 23cm splenomegaly, bilateral perinephric nodular densities and mild mesenteric and retroperitoneal lymphadenopathy. He was referred for oncologic evaluation of possible T cell hepatosplenic lymphoma.

Initial labs showed mild leukopenia with relative monocytosis and anemia (Hgb 10.5 g/dL) with normal absolute neutrophils, lymphocytes, monocytes and platelets. Additional findings included mild hyper gammaglobulinemia, and elevated ESR and CRP. PET/CT showed mild uptake in spleen SUV 2.7, patchy increased uptake throughout the marrow with SUV 4.3.

Peripheral blood showed no evidence of clonality on T cell gene rearrangements and on flow cytometry.

Hemoglobin initially normalized with iron repletion. Serial follow up imaging remained fairly stable over 18 months, though labs showed mild progressive thrombocytopenia to 90-110 k/uL range. He then developed significant anemia with absolute neutropenia of 500 and iron deficiency with occult hematuria. Iron was replaced without significant change in hemoglobin and he required intermittent transfusions. Imaging continued to show mild diffuse retroperitoneal and mesenteric lymphadenopathy with splenomegaly slightly improved to 18 cm and perinephric stranding. Perinephric biopsy showed histiocytic and fibrotic process with negative flow cytometry. Outside pathology review reported fibro-inflammatory reaction with foamy histiocytes such as xanthogranulomatous pyelonephritis or Erdheim-Chester Disorder. BRAF V600E and S100 tested negative.

Bone marrow biopsy showed hyper cellularity without fibrosis, dysplasia or obvious involvement. Cardiac MRI was most compatible with previous ischemic infarct as opposed to an infiltrative process. Since he was BRAF wild type positive he was started on peglyated interferon and is no longer transfusion dependent with improved neutropenia.

Both of these cases of Erdheim Chester Disease were somewhat atypical and difficult to diagnose despite multiple biopsies that were reviewed by multiple pathologists.

This disorder was first described in 1930s by pathologists Erdheim and Chester. This is clonal hematopoietic neoplasm of monocyte/macrophage lineage and is described as one of the Non Langerhans histiocytic disorders. These cells infiltrate bones, retro peritoneum, kidneys, pituitary gland, brain, orbits, large vessels, cardiovascular (including pericardium), lungs, pleura and skin. Presentation can be asymptomatic or symptomatic and some have fulminant clinical courses, with different organ involvements and varying presentations.[1,2]

Diaphysis and metaphyseal areas of long bones are commonly involved with sclerotic lesions in symmetrical pattern, but not seen in all.[1-3]

Since there are only a few hundred cases reported in literature, a consensus conference was held in 2013 to establish guidelines based on limited data available from case reports, and reviews. Diagnostic criteria and limited evidence based recommendations, and expert opinions were presented.[3]

Our cases both had perinephric stranding and retroperitoneal infiltration and these changes may be a clue to diagnosis. Circumferential periaortic sheathing (coated aorta) has been reported. Central Diabetes Inspidus is common and others may have pituitary stalk infiltration and cerebellar involvement and expansile enhancement of pachymeninges, and orbital masses.[1-4]

Abundance of typical histiocytes can vary in different biopsy specimens from different areas with different amount of inflammatory and stromal proliferation making diagnosis of clonal disorder difficult. Typically Langerhans histiocytes have S100 expression but 20% of ECD can have it. Also LCH are typically CD1a positive and not ECD histiocytes . Factor X111a expression is typically present in ECD only.[3-5]

Although somatic BRAF mutation is present in over 50% of cases, others may have clonal mutation in RAS-RAF-MEK-ERK - MAPK pathway (Mitogen activated protein kinase) or PI3K (Phosphoinositide 3 kinase) mutation. This helps document clonality of histiocytes to establish diagnosis and may provide therapeutic target. These mutations are present in other disorders but typically not in other non-Langerhans histiocyte disorders.[3-6]

BRAF directed drugs alone or in combinations have been used in BRAF V 6ooE mutation expressing disease but MEK inhibitor like Cobimetanib has shown responses in patients with mutations in downstream pathway. Imatinib may suppress differentiation of CD34+ stem cells into histiocytes. There is increased production of Interferon alpha, which is still used for treatment. There is increased InterLeukine1 receptor expression in these histiocytes and Anakinra, a recombinant human Inter Leukine1 receptor antagonist has shown to ameliorate ECD. Infliximab (anti-Tumor Necrosis Factor alpha antibody) and steroids have been used in this disease with increased inflammatory cytokine production. Many cytotoxic chemotherapies and Cladribine has shown responses.[4-6]

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