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Mixed Histocytosis Manifesting as Suprasellar Mass with Aortic Involvement

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Manifesting as Suprasellar Mass with Aortic Involvement

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Learning Objectives

- ❑ Define Histiocytoses, L-CH, N-LCH, and Mixed Histiocytosis
- ❑ Explain the spectrum of L-type histiocytosis
- ❑ Discuss difference in organ system involvement
- ❑ Examine difficulty in diagnosis
- ❑ Discuss importance of imaging, cytology, and clinical suspicion in diagnosis
- ❑ Review classification schema and treatment

Introduction

- ❑ Histiocytoses are group of disorders affecting myeloid progenitor cells
- ❑ The etiopathogenesis of histiocytoses are largely unknown, but BRAF-V600E mutation is frequently implicated in the pathogenesis of these conditions
- ❑ Histiocytoses are grouped into L-C-M-R-H classification presenting with various symptomology, cytology, and prognosis dependent on category
- ❑ The L-group includes Langerhan, Non-Langerhan, and Mixed histiocytosis
- ❑ Langerhan Cell Histiocytosis (LCH) incidence is one case per million adults
- ❑ Non-Langerhan Cell Histiocytosis (N-LCH) have only 500 documented cases and Mixed Histiocytosis only around 100 cases (2+ others)
- ❑ Histiocytoses clinical manifestations vary depending on organ involvement
- ❑ LCH has been known to affect long bones, skin, lymph nodes, spleen, and CNS
- ❑ N-LCH can affect long bones, maxillary sinuses, large blood vessels, heart, CNS, skin and pituitary gland (2)
- ❑ Diagnosis is made with tissue biopsy with cytology, clinical manifestations, and imaging showing multisystem involvement
- ❑ Cytology testing include CD1a, CD68, CD163, CD207, S100, BRAFV600E,
- ❑ LCH and N-LCH carry a poor prognosis, which worsens with CV and CNS involvement
- ❑ Treatment for LCH, N-LCH, and Mixed Histiocytosis vary so differentiation is important
- ❑ LCH treatment is centered off radiation, resection, and targeted chemotherapy
- ❑ N-LCH has no standardized treatment but trials show benefit with adding PEG-a unlike LCH

Table 1: LCH vs. N-LCH vs. Mixed Histiocytosis

Categories	Langerhan Cell histiocytosis (LCH)	Non-Langerhan Cell histiocytosis (N-LCH)	Mixed Histiocytosis
Epidemiology	1:1,000,000 incidence	~500 reported cases	~100 reported cases
Organ involvement	Bone, Skin, Lymph nodes, Liver, Spleen, CNS	Bone, Blood Vessels, Heart Retroperitoneum, Lung, CNS, Skin, Pituitary	More consistent with N-LCH, Bones, Vasculature
Histology	Birkbeck granules	Touton Cells Foamy histiocytes	Heterogenous combination
Cytology	CD1a+ , S100+, CD207+	(-)CD1a or CD-68+	Mixed presentation
Genetics	69% BRAF V600E (+)	82% BRAF V600E (+)	89% BRAF V600E (+)
Treatment	BRAF(+) Vemurafenib Vinblastine (+/-) Mercaptopurine Clabridine or Etoposide Radiation/Resection	No Standardized Treatment: BRAF(+) Vemurafenib **Pegylated INF-α** Radiation/Resection Note: Clabridine ineffective	Not well established: BRAF(+) Vemurafenib Radiation/Resection

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Case Presentation

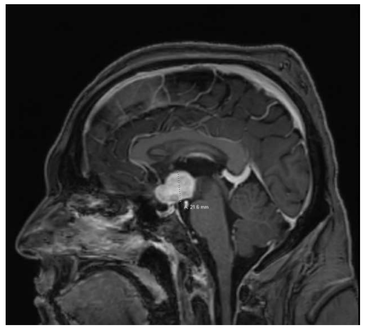
In August, A 42-year-old white female with a past medical history of migraines, depression, and fibromyalgia initially presented to Henry Ford Macomb Hospital after a syncopal event. The event occurred after having sutures removed one week status-post tenosynovitis release surgery and was transported to the ER immediately for evaluation.

Upon arrival, the patient was feeling light-headed with associated headaches, visual changes, diaphoresis and fatigue which she had not experienced in the past. The patient denied symptoms of fever, shortness of breath, nausea, vomiting, focal weakness, or loss of sensation. The patient family history and social history were both unremarkable. Her past surgical history was significant for tenosynovitis release, cholecystectomy, sleeve gastroplasty, and umbilical hernial repair. The patient has no known drug allergies. The patient medications included cetirizine, cyclobenzaprine, duloxetine, lortab, ibuprofen, ativan, omeprazole, sertraline, tizanidine, and tramadol. Physical exam was notable for an anxious woman in mild distress, appearing pale, no obvious signs of trauma, normal heart and lung sounds, no abdominal tenderness, and no focal neurologic deficits. The patients vitals revealed a blood pressure of 71/47mmHg, HR 84bpm, 97.2 °F temporally, RR 16rpm, and SpO2 96% on room air.

Initially the event was presumed to be vasovagal in nature but a syncopal workup ensued with an EKG, CTA CT head and neck, and blood work. EKG was abnormal with a prolonged QT interval of 612 which was not previously diagnosed. CTA with pulmonary embolism protocol incidentally found inflammation of the aorta and left subclavian vessel with mural thickening of descending aortic arc, CTA also showed stenosis of the celiac, superior mesenteric, and renal arteries. This finding was suspicious of Takayasu arteritis. CT head and neck revealed 14mm hypothalamic mass with optic chiasm involvement—however the patient denied visual impairment. The patient was discharged with plans to follow up with her rheumatologist and neurosurgery for evaluation of her hypothalamic mass. In December 2018, due to worsening of vision, A MRI imaging of the patients brain was obtained showing enlargement of the hypothalamic mass, measuring 21.3mm with associated intermittent horizontal diplopia occurring daily with continued fever, fatigue, and cold intolerance. Within a month, the patient had a right craniotomy preformed with partial tumor resection and was complicated by post-operative cerebral edema and uncal herniation. Patient was given Decadron and intubated for a week to preserve the airway. The patient subsequently developed diabetes insipidus which was treated with desmopressin. Endocrinology diagnosed panhypopituitarism secondary to resection and hormone replacement therapy was initiated. The patient is still being treated for her condition.

Final pathology reports revealed BRAF positive Langerhans Cell Histiocytosis, staining positive for CD1a, S-100, Langerin, CD68 and CD168. Two weeks later, the patient was discharged home after stabilization.

Clinical Imaging



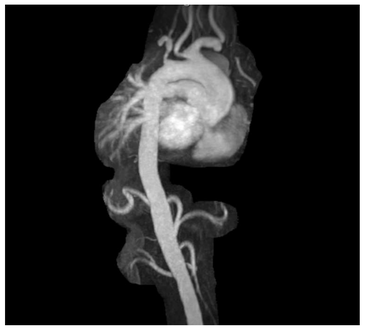


Figure 1: (above left) MRI of head
21.6mm suprasellar mass which appears to be centered on the pituitary stalk neural hypophysis
Mass effect upon the hypothalamus and optic chiasm

Figure 2 (above right): MR-Angiography of Chest/Abdomen
Multiple findings consistent with Takayasu Arteritis
Diffuse mural thickening of the aortic arch + descending thoracic aorta—thickness (6mm)
Moderate stenoses of the proximal portions of the left subclavian artery and common carotids

Laboratory Values

Table 2: Laboratory Results

Inflammatory Test	Patients Value	Reference Range	CBC labs	Patients Value	Reference Range
CRP	2.3	0-0.5 mg/dL	WBC	10.5	3.8 - 10.6 K/u
ESR	67	0-20 mm/Hr	RBC	4.71	4.15 - 5.55 M/uL
IgG-1	498	382 - 929 mg/dL	Hg	12.6	12.0 - 15.0 g/dL
IgG-2	832	242 - 700 mg/dL	Hct	37.2	36 - 46 %
IgG-3	54	22 - 176 mg/dL	Plt	390	150 - 450 K/uL
IgG-4	105	4 - 86 mg/dL			
Hormone Tests	**Patients Value**	**Reference Range**	**BMP labs**	**Patients Value**	**Reference Range**
FSH	1.9	Varies	Na+	137	135 - 145 mmol/L
LH	<.2	Varies	K+	4.5	3.5 - 5.0 mmol/L
IGF-1	44	62 - 205 ng/mL	Ca++	8.9	8.2 - 10.2 mg/dL
Prolactin	36.3	0.00 - 27.0 ng/mL	BUN	10	10 - 25 mg/dL
TSH	1.75	0.30 - 5.00 uIU/mL	Cr	.8	<1.03 mg/dL

Laboratory Values

As elucidated by this case, histiocytoses can be a difficult diagnosis and require adept clinical suspicion. Presentations vary greatly as a result of different organ involvement, from syncope from SIADH, to bone pain from lytic lesions. It is important to consider N-LCH, LCH, and Mixed histiocytosis in patients with osteolytic lesions and vascular or skin involvement. Histiocytoses can frequently inflict different organ systems thus clinical consideration should be given in patients with odd presentations that cannot be attributed to a particular cause especially when bone, skin, and vasculature are involved. In this case, the patients vascular involvement mimicked a vasculitis—Takayasu arteritis—with aortitis, subclavian, and renal artery infliction but further evaluation illustrated a histiocytosis picture.

The different and hard to recognize presentations, such as this case makes classification of histiocytoses difficult as well. The subclassifications within the L-group of LCH, N-LCH, and Mixed histiocytosis are nebulous. Cases of these conditions are exceptionally rare which make the classification system difficult to effectively distinguish. The classification of these groups are primarily cytologic, but is this the best way to classify these conditions clinically? These processes pathogenesis are widely unknown, but are known be error in myeloid progenitors differentiation—presumptively at different locations. This could provide context to why the tumors cell markers vary even amongst the same class. The biopsy for this case revealed CD-1a positive yet its CD-163/CD-68 positivity technically classifies it “Non-Langerhan Cell”. Different lesions, such as this patients, doesn’t fit distinctly into any of the three as aforementioned categories which makes the current schema seem relatively ineffective. This patients clinical presentation with vascular involvement was more consistent with N-LCH; however, the cytology was inconclusive between LCH and N-LCH—making it more consistent with mixed histiocytosis. Since cytology can be inconclusive especially in light of clinical findings, it makes the L-group of histiocytosis seem to be more of a spectrum of disease rather than distinct categories.

LCH and N-LCH are important to differentiate as their management strategies differ in approach although there treatment guidelines are not well established. It is important to to recognize that these two disease processes can occur together manifesting as “mixed histiocytosis”. In patients with mixed histiocytosis with a BRAF V600E mutation Vemurafenib is recommended non-dependent on origin. If the patient can not tolerate Vemurafenib then the patient is treated with pegylated interferon alfa or MEK inhibitor. In patients without the BRAF mutation, conventional or pegylated interferon alfa is used and followed by then Cladribine and Cyclophosphamide in patients that cannot tolerate or fail interferon-a. Patients are often encouraged to enroll in clinical trials as there is not many set guidelines of treatment due to the rare nature of disease.

Conclusion

- ❑ Histiocytoses present as a rare spectrum of disease with different presenting symptoms
- ❑ Differences in diagnosis depends primarily on cytology and organ system involvement
- ❑ Treatment protocols vary for different histiocytosis although guidelines are not well established
- ❑ Patients that present under these rare condition should consider enrolling in clinical trials