Clinical History

MRI:
Post-contrast
T1-weighted

- Enlarging 17 mm well-circumscribed, solidly-enhancing nodule adjacent to R lateral ventricle
- Separate 3 mm enhancing focus
- T1 and T2 hypo- to iso-intense
- Avid enhancement after contrast injection, suggesting high N:C ratio
MRI:
T2-weighted

- Moderate perilesional vasogenic edema
- Mass effect on ventricle
Right Parieto-Occipital
Gross Total Resection
Large Cells Negative For:

- Pankeratin
- S100
- Mart1
- GFAP
- EMA
- CD45

- CD3
- CD20, PAX5
- CD138
- $\kappa/\lambda$: no restriction
- CD15
- CD30
- ALK
- CD56
- EBV EBER
CD163
CD163+, CD68+, CD4+, fascin+ profile & morphology strongly suggested a histiocytic disorder

However, the differential included monocytic disorders

Lysozyme, CD117, CD34, MPO negative: unlikely monoblastic/monocytic or myelomonocytic sarcoma

Within the histiocytic disorders, the following were ruled out:

CD1a, Langerin negative: unlikely Langerhans

CD21, CD35, CD23 negative: unlikely follicular dendritic cells

S100 negative: unlikely Rosai-Dorfman, interdigitating dendritic cells

No hemophagocytosis: unlikely hemophagocytic d/o

No xanthomatous Touton giant cells: unlikely spectrum of xanthogranulomatous d/o
overall Ki-67 labeling index was estimated at 15-20%
Infectious Work-Up

- GMS and AFB negative
- Adenovirus, CMV, and HSV I&II immunohistochemical stains negative
46,Y,der(X)inv(X)(p11.2q24)t(X;18)(q24;q11.2)[7]

Abnormal clone (7/20) with pericentric inversion of chromosome X at bands p11.2 and q24 & reciprocal translocation between chromosomes Xq and 18q, which has not been reported as a consistent finding in solid tumors
ish der(X)t(X;18)((q24;q11.2)(SYT+)
No rearrangement of the SYT gene-specific locus seen by metaphase FISH with an 18q11.2 break-apart probe, ruling out synovial sarcoma
Final Diagnosis

Primary CNS histiocytic sarcoma, presenting as a post-radiation sarcoma
## The Confusing History of Histiocytic Tumors

<table>
<thead>
<tr>
<th>Original diagnosis</th>
<th>Currently considered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histiocytic lymphoma, nodular and diffuse</td>
<td>Diffuse large B-cell lymphoma</td>
</tr>
<tr>
<td></td>
<td>Follicular lymphoma, grade 3</td>
</tr>
<tr>
<td></td>
<td>Peripheral T-cell lymphoma</td>
</tr>
<tr>
<td></td>
<td>Histioyte-rich variants of B-cell, T-cell and Hodgkin lymphoma</td>
</tr>
<tr>
<td></td>
<td>Anaplastic large cell lymphoma (ALCL)</td>
</tr>
<tr>
<td>Histiocytic medullary reticulosis</td>
<td>Haemophagocytic syndromes</td>
</tr>
<tr>
<td>Malignant histiocytosis</td>
<td>ALCL</td>
</tr>
<tr>
<td></td>
<td>Haemophagocytic syndromes</td>
</tr>
<tr>
<td>Regressing atypical histiocytosis</td>
<td>Primary cutaneous CD30 positive T-cell lymphoma</td>
</tr>
<tr>
<td>Intestinal malignant histiocytosis</td>
<td>Enteropathy-type T-cell lymphoma</td>
</tr>
<tr>
<td>Histiocytic cytopathic panniculitis</td>
<td>Subcutaneous panniculitis-like T-cell lymphoma with haemophagocytosis</td>
</tr>
</tbody>
</table>

Swerdlow et al. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues 2008.* (p355)
What Are Histiocytes?

- Histiocytes are defined as:
  - Mononuclear cells derived from BM monocytes
  - High lysosomal content

- Histiocytes include:
  - Macrophages: phagocytosis & antigen processing
  - Dendritic cells: non-phagocytic; antigen presentation & accessory support
    - Langerhans dendritic cells
    - Dermal dendritic cells
    - Interdigitating dendritic cells
    - Plasmacytoid dendritic cells
    - Follicular dendritic cells

http://nih.techriver.net/view.php?patientId=95
Macrophage

- Lymph node sinuses, medullary cords, germinal centers

http://www.udel.edu/biology/Wags/histopage/colorpage/cly/clycmln.GIF
Langerhans Dendritic Cells

- Epidermis & mucosa
- When activated, home to paracortical/T cell zone of cutaneous draining lymph nodes

https://www.ipath-network.com/inctr/object/view/4264
Dermal Dendritic Cells

- Papillary dermis
- FXIIIa
- Immature DC phenotype (CD1b+)
- Release proinflammatory cytokines
- Antigen presentation

Interdigitating Dendritic Cells

- Paracortex
- Present antigens to T-cells

Follicular Dendritic Cells

- Primary & secondary follicles
- Present antigens to B-cells
- Long-living cells involved in immunologic/humoral memory

Plasmacytoid Dendritic Cells

- Paracortex
- Produce type-1 IFN's (IFNα)
  - Enhances NK–mediated cytotoxicity
  - Recruits macrophages

### Table 14.02. Immunophenotypic markers of non-neoplastic macrophages and dendritic cells

<table>
<thead>
<tr>
<th>Marker</th>
<th>LC</th>
<th>IDC</th>
<th>FDC</th>
<th>PDC</th>
<th>Mø</th>
<th>DIDC</th>
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<tbody>
<tr>
<td>MHC-Class II</td>
<td>+c</td>
<td>++s</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
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<tr>
<td>Fc-receptors</td>
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<td>-</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>CD1a</td>
<td>++</td>
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<td>-</td>
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<tr>
<td>CD4</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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</tr>
<tr>
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<td>-</td>
<td>++</td>
<td>-</td>
<td>-</td>
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<tr>
<td>CD68</td>
<td>+/-</td>
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<td>-</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>CD123</td>
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<td>-</td>
<td>++</td>
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</tr>
<tr>
<td>CD163</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Factor 13a</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Fascin</td>
<td>-</td>
<td>++</td>
<td>+++</td>
<td>-</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Langerin</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>Lysozyme</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
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<tr>
<td>S100</td>
<td>++</td>
<td>++</td>
<td>+/-</td>
<td>-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>TCL1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
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</tr>
<tr>
<td>CD45</td>
<td>Weak+</td>
<td>Weak+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

FCR, Fc IgG receptors (include CD16, CD32, CD64 on some cells); LC, Langerhans’ cell; IDC, interdigitating dendritic cell; FDC, follicular dendritic cell; PDC, plasmacytoid dendritic cell; Mø, macrophage; DIDC, dermal/interstitial dendritic cell; c, cytoplasmic; s, surface;

Expression is semiquantitatively graded 0 through ++, + present, ++ high, +/- low or varies with cell activity.
Ontogenic Classification of Histiocytic Disorders

Swerdlow et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues 2008. (p354)

- Langerhans cell histiocytosis
- Interdigitating dendritic cell sarcoma
- Blastic plasmacytoid dendritic cell neoplasm
- Hemophagocytic syndromes
- Rosai-Dorfman
- Histiocytic sarcoma
- Juvenile xanthogranuloma
- Acute monocytic leukemia
- Fibroblastic reticulum cell sarcoma
- Follicular dendritic cell sarcoma
WHO 2008 Classification

- Macrophage/histiocytic neoplasms
  - Histiocytic sarcoma
- Dendritic cell neoplasms
  - Langerhans cell histiocytosis
  - Langerhans cell sarcoma
  - Interdigitating dendritic cell sarcoma
  - Follicular dendritic cell sarcoma
  - Fibroblastic reticular cell tumor
  - Indeterminate dendritic cell tumor
- Dermal dendritic cells neoplasms
  - Disseminated juvenile xanthogranuloma
Classification of Histiocytic Disorders

1997 WHO Committee on Histiocytic/Reticulum Cell Proliferations & Reclassification Working Group of the Histiocyte Society

- Varied biological behavior
  - Dendritic cell-related
    - Langerhans cell histiocytosis
    - Secondary dendritic cell process
    - Juvenile xanthogranuloma
    - Solitary histiocytomas with dendritic cell phenotype
  - Macrophage-related
    - Hemophagocytic syndromes
      - Primary hemophagocytic lymphohistiocytosis
      - Secondary hemophagocytic syndromes
    - Rosai-Dorfman disease
    - Solitary histiocytoma with macrophage phenotype

- Malignant
  - Monocyte-related
    - Extramedullary monocytic sarcoma
    - Acute monoblastic/monocytic leukemia (M5A, 5B)
    - AMML (M4)
    - AML with inv(16)
    - CMML
  - Dendritic cell-related histiocytic sarcoma
    - Langerhans cell sarcoma
    - Follicular dendritic cell sarcoma
    - Interdigitating dendritic cell sarcoma
  - Macrophage-related histiocytic sarcoma
Histiocytic Sarcoma

- **WHO:** malignant neoplasm of mature tissue histiocytes
- Histopathology described in the literature is very similar to our current case
- Importantly, histopathology not particularly distinctive - IHC & molecular studies essential
CNS Histiocytic Sarcoma

- Differ morphologically from other sites
- Neoplastic cells obscured by heavy inflammatory infiltrate of neutrophils, lymphocytes, plasma cells, with multiple foci of microabscess, fibrin, necrosis
- Mimicks an inflammatory process
Criteria for Diagnosis

- Requires ≥1 histiocytic marker
- CD163: hemoglobin scavenger receptor, exclusively in monocytic/histiocytic lineage
- Lysozyme, CD68, CD4, CD11c, CD14, α1-antichymotrypsin, α1-antitrypsin, MAC387, HAM56, Ki-M8, Ki-M4, cathespin D & E, M-CSF receptor
  - Less specific
  - CD68: angiosarcoma, melanoma, granular cell tumor, carcinoma, some lymphomas, schwannoma, AML without monocytic differentiation, Langerhans cell tumor, juvenile xanthogranuloma, blastic plasmacytoid dendritic cell neoplasm, interdigitating dendritic cell proliferation
Criteria for Malignancy

1. Clonal cytogenetic abnormality
2. Aneuploidy
3. Monoclonality
4. Malignant morphology
5. High proliferative rate
6. Tumorigenicity
7. Aggressive clinical course
DDX: Other Hematopoietic Neoplasms

- **Monoblastic/monocytic or myeloid sarcoma**: myeloperoxidase, CD117, CD34
- **Primary DLBCL of CNS, T/histiocyte-rich large B-cell lymphoma**: CD20, CD79a, PAX5, κ/λ, IgH rearrangement
- **Anaplastic large cell lymphoma**: CD3, other T cell markers, CD30, ALK, TCRγ rearrangement, t(2;5) NPM/ALK
  - Pitfall: neoplastic cells may express CD68, CD11b, α1-antichymotrypsin, lysozyme
- **Peripheral T-cell lymphoma, lymphoepithelioid variant (Lennert lymphoma)**: CD3, CD8, CD56, cytotoxic granules, EBV+ Reed-Sternberg-like cells
- **Hodgkin lymphoma**: Pax5, CD15, CD30
- **Plasma cell neoplasms**: CD138, κ/λ
DDX: Other Histiocytic Disorders

- **Dendritic cell disorders:**
  - **Langerhans cell neoplasms:** CD1a, langerin, S100, Birbeck granules
  - **Follicular dendritic cell sarcoma:** CD21, CD35, CD23, clusterin, desmosomes & cytoplasmic processes by EM
  - **Interdigitating dendritic cell sarcoma:** S100, interdigitating cell processes by EM
  - **Juvenile xanthogranuloma etc:** pathognomonic Touton giant cells, FXIIIa, CD68, fascin
  - **Erdheim-Chester:** pathognomonic bilateral symmetrical osteosclerosis of metaphyses/diaphyses of long bones with sparing of epiphyses, lipid-laden foamy histiocytes, FXIIIa, CD68, fascin

- **Other macrophage disorders:**
  - **Hemophagocytic syndromes:** hemophagocytosis, clinical (cytopenias, fever, ↑ spleen, ↑ triglyceride, ↓ fibrinogen, ↑ plasma soluble IL2 receptor)
  - **Rosai-Dorfman:** dural, emperipolesis, S100
  - **Reticulohistiocytoma/sis:** ground-glass histiocytes
DDX: Non-Hematopoietic Neoplasms

- **Pleomorphic xanthoastrocytoma:** characteristic imaging with circumscribed solid & cystic mass or a cyst with mural nodule, GFAP (100%), S100 (100%)
  - Pitfall: often CD68+

- **Gliosarcoma:** areas of typical glioblastoma
  - Pitfall: sarcomatous area GFAP-

- **Lymphoplasmacyte cell-rich meningioma:** EMA, vimentin

- **Inflammatory myofibroblastic tumor:** ALK, 2p23 rearrangement

- **Carcinoma:** pan-cytokeratin, CAM5.2

- **Melanoma:** S100, HMB45, melanA
DDX: Infectious, Inflammatory

- **Infection:** viral inclusions, fungus, parasites/protozoa, microbiology workup
- **Mycobacterium avium-intracellulare** spindle-cell pseudotumor: AFB
- **Subacute infarct:** Red neurons, liquefactive necrosis
- **Tumefactive demyelination:** Macrophages with Luxol fast blue/PAS+ myelin breakdown products
- **IgG4-related sclerosing disease:** IgG4/IgG > 40%, obliterative phlebitis
- **Idiopathic hypertrophic pachymeningitis**
- **Inflammatory pseudotumor**
Prognosis

- In general, poor prognosis: 60–80% die of progressive disease within 1 year

- Primary CNS HS also appears to have poor prognosis
  - 6 total cases reported
  - 5 cases:
    - Median survival 4.5 months
    - Metastases to serosal surfaces, mediastinum, bone
  - 1 case: initial indolent course with response to resection & radiation, followed by subsequent relapse to the mediastinum 3½ years later
  - Current case: disease recurrence 1 year after resection & radiation, recurrent disease unresponsive to salvage chemotherapy
References


References


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