**1. Title - Diffuse histiocytic sarcoma involving the choroid: a case report**

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**2. Case Report**

A middle-aged male was admitted to a regional hospital with acute sinusitis, tonsillitis, increasing dysphagia and dyspnea. Recently he had been investigated for malaise, generalized lymphadenopathy and anemia. The patient presented to Ophthalmology for painless left blurred vision. On examination, he had a left central scotoma but 6/6 vision in both eyes. Subtle left subretinal fluid, consistent with central serous chorioretinopathy (CSCR), was noted on fundoscopy and confirmed on ocular coherence tomography (OCT). There was no intraocular inflammation; thus management involved observation. Meanwhile, histological examination of nasal-and bone-marrow biopsies revealed the diagnosis of HS.

The patient was rapidly transferred to the RLBUHT for chemotherapy. Following transfer, he was seen in the LOOC for bilateral painless vision loss. Visual acuity was 6/9 OD; 6/18 OS. Examination revealed ‘quiet’ eyes with no inflammation but bilateral focal macular retinal detachments (RDs; Fig.1A&B). Systemic PET-CT showed disseminated HS with widespread increased FDG uptake in lymph-nodes and bone-marrow. Head MRI showed enlarged adenoids, parotids and clival involvement.

The patient deteriorated under chemotherapy, succumbing to systemic HS within 3-weeks of admission. Informed consent was obtained from relatives for autopsy, and to use tissue for research according to the Declaration of Helsinki. The left eye was sent for histopathology. Complete autopsy findings are not presented here, however, extensive HS infiltration of numerous organs was observed.

The left globe was intact with normal dimensions and no shadow seen on transillumination. The choroid was filled by HS cells (Fig.1C); which were medium-to-large with abundant cytoplasm and prominent large round-to-oval/folded nuclei (Figs.1D&E). On immunohistochemistry, HS cells expressed histiocytic-markers CD163 (Fig.1F), CD68 (Fig.1G), and lysozyme. They were negative for Langerhans-cell-, follicular dendritic-cell-, myeloid-cell-and lymphocytic-markers (Fig.1H). The Ki-67 growth-fraction was 10% (Table1).

Cytogenetics of HS cells demonstrated polysomy of chromosomes (chr) 7 and 8. Single-nucleotide-polymorphisms microarray results showed additional changes: partial deletion chr1p; chr9 duplication; loss of chr4, 14 and 15. Analysis for clonal immunoglobulin and T-cell receptor gene rearrangements was negative; similarly, NPM1 translocation was negative.

**3. Discussion**

Histiocytic sarcoma (HS) is an extremely aggressive and rare hematopoietic neoplasm; its exact incidence is unknown.1 To our knowledge, this is the first documented case of intraocular involvement by HS in a human eye. Interestingly although extensive choroidal infiltration by HS cells was seen histologically, clinically, there was no ocular inflammation only a serous RD with OCT findings of CSCR.

Inconsistencies in terminology and diagnostic criteria have complicated HS’s recognition and characterization. 2 Cases of HS reported prior to 1990 were likely to be misdiagnosed. 3 The term ‘histiocytic sarcoma’ was introduced in 1970 and descriptions were based strictly on histological similarities of the cells to macrophages. 4 Subsequently, increasing emphasis was placed on distinct immunohistochemical criteria of HS cells to demonstrate their histiocytic lineage. At present, HS diagnosis is one of exclusion and is based on histopathological features (atypical histiocytic morphology) associated with immunoreactivity for one or more histiocytic-markers (mainly CD163), in absence of follicular dendritic-cell and myeloid-markers. 5 The 2001 WHO definition of HS required absence of clonal B/TCR gene rearrangements, inorder to differentiate HS from lymphomas. However, the 2008 WHO classification recognized that unusual HS can arise secondary to or concurrently with B-or T-lymphoblastic lymphoma/leukemia or mature B-cell neoplasms, and therefore could demonstrate clonality. 2 In our case, morphological, immunohistochemical and molecular genetic criteria were fulfilled to confirm the unequivocal diagnosis of HS.

In conclusion, this case demonstrates choroidal involvement by HS in the human eye confirmed immunohistochemically and genetically. Interestingly, extensive uveal infiltration was noted in absence of inflammation, with serous RD observed clinically, which is more commonly associated with metastatic carcinomas or choroidal lymphomas. 6

**4. Acknowledgements**

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**6. Table 1:** Immunophenotypic profile of HS versus dendritic cell tumors and other mimicking neoplasms.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | LCT/S | IDCT/S | FDCT/S | DCS -NOS | HS | Melan | DLBCL | ALCL | Our case |
| CD68 | + | + | + | + | + | - | - | - | + |
| Lysozyme | -/+ | - | - |  | + | - | - | - | + |
| CD163 |  |  |  |  | + | - | - | - | + |
| CD1a | + | - | - | + | - | - | - | - | - |
| CD21/CD35 | - | - | + |  | - | - | - | - | - |
| S-100 | + | + | -/+ | + | -/+ | + | - | - | -/+ |
| HMB45 | - | - | - | - | - | + | - | - | - |
| Melan A | - | - | - | - | - | + | - | - | - |
| CD30 | - | - | - | - | - | - | -/+ | + | - |
| CD20 | - | - | - | - | - | - | + | - | - |
| ALK-1 | - | - | - | - | - | - | -\* | +/- | - |

Abbreviations: LCT/S: Langerhans cell tumor/sarcoma; IDCT: Interdigitating cell tumor/sarcoma; FDCT: Follicular dendritic cell tumor/sarcoma; DCS: Dendritic cell sarcoma not-otherwise specified; Melan: Melanoma; DLBCL: Diffuse large B cell lymphoma; ALCL: Anaplastic large cell lymphoma \* rare subtype of ALK+ DLBCL

*Reactivity: +: 75-100%; +/- 50-75%; -/+: 25-50%; rare: 10-25%, -: <10%*

**7. Figure Title: OCT findings and immunohistochemistry (IHC) results.**

**Figure Legend**

Fig. 1:

1A&B) OCT images OD and OS, respectively; 1C) Choroidal infiltration by HS (Ch), sclera (S), retina (R) and optical-nerve (ON) were tumor-free (H&E,4X); 1D) Choroidal infiltration by HS (H&E,20X); 1E) Neoplastic-cells showed prominent/convoluted nuclei, in choroidal blood-vessels (arrows) (H&E,40X); 1F) HS cells are CD163+ (brown,25X); 1G) CD68+; 1H) HS cells were negative for: Langerhans-cell-(CD1a,Langerin), follicular-dendritic-cell-(CD21,CD35), myeloid-cell-(myeloperoxidase, CD33, CD13), lymphoid-cell-markers (CD3,CD20,CD79a,Pax5) and Melan A (Note:choroidal melanocytes between negative tumor-cells).