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Cytophagic histiocytic panniculitis with fatal haemophagocytic lymphohistiocytosis in a paediatric patient with perforin gene mutation

Cytophagic histiocytic panniculitis (CHP), or histiocytic cytophagic panniculitis, is a rare form of panniculitis associated with haemorrhagic diathesis and histiocytic lymphohistiocytosis (HLH), initially described in 1980 as a benign lymphoproliferative disease.¹ In 1991 Gonzalez *et al* reported a unique entity of subcutaneous T-cell lymphoma with haemophagocytosis, later designated as subcutaneous panniculitis-like T-cell lymphoma (SPTL).² Marzano *et al* suggested that CHP and SPTL might span a clinicopathological spectrum in which there is a natural progression from CHP to SPTL.³ HLH is a clinical syndrome of immune deregulation with hypercytokinaemia causing dysfunctions of various organs and a high mortality. Familial HLH (FHL) is associated with several hereditary defects. Stepp *et al* first showed that the mutation in perforin gene (*PRF1*) at chromosome 10q21 was responsible for 20–40% of FHL patients.⁴

Case report

An 11-year-old girl with CHP and HLH presented with spiking fever and indurated skin nodules over the left thigh (fig 1A). She had psychomotor retardation and spastic type cerebral palsy at 2 years of age and epilepsy at age 7. Physical examination revealed indurated skin nodules and hepatosplenomegaly without lymphadenopathy. Laboratory tests showed anaemia, thrombocytopenia, impaired liver function, and raised triglyceride level, without coagulopathy. Blood and urine cultures were negative. Her fever and skin lesions responded dramatically to prednisolone and intravenous immunoglobulins. She became prednisolone-dependent despite attempts at tapering off by adding methotrexate and cyclosporine A. Several episodes of HLH and infections led to three additional admissions in three years. Six months later, she developed prominent facial bruising and swelling. Virological surveys revealed prior/remote Epstein-Barr virus (EBV) infection without infection by hepatitis viruses A, B, C, or cytomegalovirus. Whole body CT scans revealed brain atrophy, pericardial effusion, and ascites without lymphadenopathy. Three courses of 13-cis retinoic acid with prednisolone led to regression of skin lesions. Unfortunately, she developed spiking fever and died of coagulopathy with acute abdominal bleeding and hypovolaemic shock, four years after initial presentation.

Pathological and molecular genetic findings

The skin biopsies at presentation and at 3 years revealed significant lobular panniculitis with

Figure 1 (A) Photograph showing plaques and nodules on both thighs. (B) Photomicrograph showing a lymphohistiocytic infiltration involving predominantly subcutaneous fat with one bean bag-histiocyte in the centre (H&E); inset shows a bean bag-histiocyte highlighted by anti-CD68 (immunohistochemical staining). (C) Photomicrograph showing small lymphocytic infiltration in a lace-like fashion rimming fat spaces with high-power in the inset (H&E). The majority of these infiltrating lymphocytes express: (D) T-cell intracellular antigen-1 (immunohistochemical stain for T-cell intracellular antigen-1) and granzyme B; (E) with only a few cells expressing perforin (immunohistochemical stain for perforin). (F,G) Photomicrograph at autopsy showing florid haemophagocytosis in the marrow (F) and late-stage neurodegenerative changes in the frontal grey matter with marked neuronal loss and increased number of reactive astrocytes indicated by arrows (G) (H&E). Parental/guardian informed consent was obtained for publication of this figure.

small lymphocytic infiltration within the lobular septa and around the individual fat cells, with occasional benign histiocytes showing haemophagocytosis (fig 1B). These small lymphocytes exhibited slightly irregular nuclear contours with hyperchromasia (fig 1C). Immunohistochemically, nearly all the infiltrating lymphocytes expressed CD2, CD3, CD5, CD7, CD8, T-cell intracellular antigen-1 (fig 1D), and granzyme B, but not CD4 or CD56. Repeated immunostainings showed that the majority of the lymphocytes were negative for perforin (fig 1E). These infiltrating lymphocytes were negative for EBV by in situ hybridisation. Clonality study using paraffin sections from skin biopsy with PCR for T-cell receptor- γ chain (TCR γ) gene rearrangement was performed in duplicate with appropriate controls; the result was polyclonal. Bone marrow aspirations at presentation and at 3 years revealed histiocytic haemophagocytosis, with the latter showing more significant haemophagocytosis and T-cell infiltration.

At autopsy she was 45.5 kg and 137 cm with moon face, ecchymosis, ulcerated plaques in the extremities, bloody ascites, enlarged liver (1750 g) and spleen (180 g). Sections revealed lobular panniculitis and fulminant haemophagocytosis in liver and bone marrow (fig 1F) without lymphoma. Sections of the brain revealed prominent neuronal loss with gliosis and spongiosis in the cortex of the frontal (fig 1G), temporal, parietal, and occipital lobes, consistent with a late-stage neurodegenerative process. Cloning and sequencing for *PRF1* using DNA extracted from bone marrow at diagnosis as previously described⁵ showed a heterozygous nonsense point mutation with 1168 C>T (Arg390stop) (fig 2). The same assay using peripheral blood from the patient's healthy mother and only sister was negative.

Discussion

To our knowledge, there has been no genetic study on patients with CHP associated with HLH. Recent progress has clarified four types of

Figure 2 Sequencing of the *PRF1* gene with genomic DNA extracted from the bone marrow mononuclear cells from the patient at presentation shows heterozygous point mutation at 1168 C>T(Arg390stop) in the upper panel (A), while the other allele at the lower panel is normal (B).

FHL with specific underlying molecular alterations: FHL1 (unidentified gene located at 9q21–22), FHL2 (*PRF1* at 10q21), FHL3 (*UNC13D* at 17q25), and FHL4 (*STX11* at 6q24).⁴ In the majority of FHL2 cases, *PRF1* abnormality has been identified as homozygous mutations or as compound heterozygous mutations, with exceptional cases showing a single allele heterozygous mutation as in our patient.^{5,6} The *PRF1* mutation at 1168 C>T (Arg390stop) was previously identified in a Japanese FHL patient, who had another mutation of 1090–1091delCT as a compound heterozygous mutation (IU and SI, unpublished observations). The psychomotor retardation with cerebral palsy, epilepsy, and neuropathy at autopsy suggests that our patient might be a victim of FHL, which carries a high incidence of CNS lesions.⁷ Furthermore, immunohistochemical staining confirmed the defect in the expression of perforin by cytotoxic T cells. The alternative explanation is that her CHP is a new form of the heterozygous *PRF1* mutation-related haematological disorders such as lymphoma, leukaemia, and aplastic anaemia.^{8–10} It would be interesting to study *PRF1* mutations in patients with CHP and SPTL in the future, ideally including perforin expression and functional cytotoxic T lymphocyte assays.

Previously, Craig *et al* found that some SPTL appear to EBV-associated, with malignant histopathology, and with terminal dissemination in a rapidly fatal progression.¹¹ However, classic CHP without proven lymphoma may be EBV-unrelated, with benign histology, and an indolent course unless developing terminal HLH. In our patient, the polyclonal EBV-negative T-cells without aberrant antigen loss and absence of lymphoma at autopsy indicate that she had a benign, classic CHP with fatal HLH rather than SPTL. Classical, benign CHP is a non-neoplastic disorder, yet this disease is usually fatal due to HLH and coagulopathy. We chose to use 13-cis-retinoic acid in this patient as it has been effective in patients with cutaneous lymphomas other than mycosis fungoides.¹² However, this agent offered only a transient response in our patient. Since the

distinction of CHP from SPTL is difficult and CHP might be a precursor of SPTL, Wick and Patterson suggested using the term “panniculitis-like subcutaneous lymphoma with cytophagocytosis” instead of CHP if strict clinicopathological criteria have been met, even without documented T-cell monoclonality.¹³ This approach would have a beneficial effect on treatment planning towards oncological rather than anti-inflammatory therapy. In line with that suggestion, Pettersson *et al* reported that three of their four CHP patients responded to immunosuppressive or cytostatic drugs.¹⁴ Considering the aggressive/refractory disease, part of which might be related to her *PRF1* mutation, our patient might have benefited from high-dose chemotherapy followed by autologous peripheral blood stem cell transplantation as suggested for the treatment of aggressive CHP.¹⁵

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Hamazaki-Wesenberg bodies in two patients with no history of sarcoidosis

Patient A

A 76-year-old woman underwent a left nephrectomy for a retroperitoneal angiomyolipoma, which was contacting and displacing the spleen and left kidney. Intraoperative frozen sections of a periportal lymph node revealed brown pigment within the sinuses. Permanent sections of this specimen demonstrated a reactive lymph node with lipogranuloma formation, prominent histiocytes, and ovoid, dark-brown to yellow structures located within the sinuses, associated with the prominent histiocytes. These structures ranged from 0.25–1.0 times the size of a lymphocyte nucleus and were primarily extracellular, with only occasional examples noted within histiocytes.

Patient B

A 55-year-old man underwent a right hemicolectomy for a tubulovillous adenoma of the ascending colon. Preoperative CT scan revealed