Brief report

ALK⁺ histiocytosis: a novel type of systemic histiocytic proliferative disorder of early infancy

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We report 3 cases of a previously uncharacterized form of histiocytosis presenting in early infancy and showing ALK immunoreactivity. The patients presented with pallor, massive hepatosplenomegaly, anemia, and thrombocytopenia. Liver biopsy showed infiltration of the sinusoids by large histiocytes with markedly folded nuclei, fine chromatin, small nucleoli, and voluminous lightly eosinophilic cytoplasm that sometimes was vacuolated or contained phagocytosed blood cells. One patient developed cutaneous infiltrates that morphologically resembled juvenile xanthogranuloma. The histiocytes were immunoreactive for histiocytic markers (CD68, CD163, lysozyme), S100 protein, ALK (membranous and cytoplasmic pattern), and dendritic cell markers (fascin, factor XIIIa), but not CD1a and langerin.

Results and discussion

Clinical features

The 3 female infants presented with pallor (Table 1). All had prominent hepatosplenomegaly, but no fever. There was marked anemia and thrombocytopenia, but no leucopenia. Marrow examination showed no obvious abnormal infiltrate or hemophagocytosis. Serologic studies for the common viruses and Toxoplasma were negative. Clinically, storage disease and malignancy were suspected, prompting performance of liver biopsy. Cases 1 and 2 were given dexamethasone and etoposide, whereas case 3 was not given any specific treatment. The hematologic pictures improved slowly over many months, and the hepatosplenomegaly also gradually resolved. The patients were well at 2.5 to 7 years, and showed normal development.

Pathologic findings

The liver biopsies of all 3 cases showed sinusoidal infiltration by single or small aggregates of histiocytes. The histiocytes were very large, with irregularly folded or lobulated nuclei, fine chromatin, and small nucleoli; some contained 2 to 4 nuclei. The voluminous eosinophilic cytoplasm often contained small vacuoles, and occasionally phagocytosed lymphocytes, polymorphs, normoblasts, red cells, or hemosiderin (Figure 1A-C). In case 1, histiocytes also

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formed aggregates in the portal tracts. Ultrastructural studies were available in cases 1 and 2, and showed cells with short cell processes and abundant cytoplasm containing mitochondria, rough endoplasmic reticulum, ribosomes, lysosomes, and phagolysosomes, but not Birbeck granules. There was no ultrastructural evidence of metabolic disease.

The skin biopsy of case 1 showed a noncircumscribed dermal lesion resembling early juvenile xanthogranuloma predominated by nonlipidized cells. The lesional cells were similar to those seen in the liver, but were admixed with occasional multinucleated giant cells with wreathlike nuclei but that lacked the peripherally located vacuoles characteristic of Touton giant cells (Figure 1D).

In all 3 cases, the lesional cells in the liver showed strong positive staining for CD68 (PGM1; Dako, Glostrup, Denmark), CD163 (10D6; Novocastra, Newcastle upon Tyne, United Kingdom), and lysozyme (antiserum; Dako) (Figure 1E); heterogeneous staining for S100 protein (antiserum; Dako), langerin (12D6; Novocastra), CD20 (O10; Novocastra), and CD3 (PS1; Novocastra), and CD30 (BerH2; Dako) were negative. The Ki67 (antiserum; Dako) proliferative index was low (<2%).

Marrow biopsies were available for ALK immunostaining in cases 2 and 3; these biopsies were originally interpreted on retrospectively on ALK staining. The presence of liver and muscle biopsies of case 1, suggesting presence of t(1;2)(q25;p23).10 The test was unsuccessful in case 2, presumably due to RNA degradation, and there was insufficient material in case 3 for the study.

**Occurrence of ALK translocation**

Primary systemic anaplastic large cell lymphoma commonly exhibits a unique t(2;5) or variant chromosomal translocation, with ALK gene fused with a housekeeping gene, such as NPM, TPM3, and TFG, resulting in expression of ALK protein.12-15 Currently, only 3 other tumor types are known to exhibit ALK translocation and ALK expression—ALK+ large B-cell lymphomas, inflammatory myofibroblastic tumors, and less than 5% of non–small cell lung carcinomas.16-23 This report expands the spectrum to include ALK+ histiocytosis. In all these proliferations, the formation of X-ALK homodimers/polymers using dimerization sites at the N-terminus of ALK partners mimics ligand binding, and is responsible for activation of the ALK catalytic domain and oncogenic properties of the fusion protein.12

**ALK+ histiocytosis as a distinctive disease**

We propose the designation “ALK+ histiocytosis” for this distinctive entity presenting in early infancy, characterized by proliferation of morphologically distinctive histiocytes with unique expression of ALK. The presence of liver and subcutaneous features indicates that the disease is systemic. Features suggesting that the histiocytes are macrophages include the following: presence of phagocytosis; immunoreactivity for CD163, a histiocytic marker

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**Table 1. Summary of clinical findings**

<table>
<thead>
<tr>
<th>Case; sex/age</th>
<th>Case 1; F/neonate</th>
<th>Case 2; F/3 mo</th>
<th>Case 3; F/3 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Presentation</strong></td>
<td>Pallor; failure to thrive; abdominal distension; ascites; lower limb edema</td>
<td>Pallor; mild jaundice</td>
<td>Noted to have persistent pallor on regular checkup</td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
<td>Gross (liver 11 cm and spleen 9 cm below costal margin)</td>
<td>Gross (liver 6 cm and spleen 4 cm below costal margin)</td>
<td>Demonstrated on ultrasound examination; a 2-cm hypodense area in dome of liver on CT scan</td>
</tr>
<tr>
<td>Blood counts</td>
<td>Hb level: 4.3 g/L; Platelet count: 3 × 10^9/L</td>
<td>Hb level: 34 g/L; Platelet count: 12 × 10^9/L</td>
<td>Hb level: 63 g/L; Platelet count: 57 × 10^9/L</td>
</tr>
<tr>
<td>Serum albumin level</td>
<td>15 g/L</td>
<td>19 g/L</td>
<td>NA</td>
</tr>
<tr>
<td>Serum ferritin level</td>
<td>361 μg/L</td>
<td>1060 μg/L</td>
<td>NA</td>
</tr>
<tr>
<td>Serum triglycerides</td>
<td>1.7 mM</td>
<td>1.9 mM</td>
<td>NA</td>
</tr>
<tr>
<td>Plasma fibrinogen</td>
<td>3.3 g/L</td>
<td>3.93 g/L</td>
<td>NA</td>
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<tr>
<td>Treatment and outcome</td>
<td>Mechanical ventilation for increased ascites impairing breathing. Given dexamethasone and etoposide for about 8 months. Anemia gradually improved, platelet count rose, and biochemical profile normalized. Second biopsy was taken at 1 year (reported then as normal, but abnormal histiocytes were identified retrospectively on ALK immunostaining), and no further treatment was given. Well, with normal growth at 5 years.</td>
<td>Given dexamethasone and etoposide for about 8 months. Anemia gradually improved, platelet count rose, and biochemical profile normalized.</td>
<td>Empirically treated with antibiotics. The hemoglobin gradually dropped further, and platelet count remained on the low side. Progressive increase in size of liver (12 cm) and spleen (3 cm). No specific treatment given. Then, condition gradually improved, hepatosplenomegaly regressed, and blood counts normalized. Well at 7 years.</td>
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None of the patients had fever. N indicates normal range; CT, computed tomography; and NA, not available.
not expressed on dendritic cells; and ultrastructural features of phagocytic cells. On the other hand, positive staining for factor XIIIa and fascin suggests a relationship with dendritic cells. Thus, the macrophage versus dendritic cell lineage of ALK+ histiocytosis remains to be clarified.

ALK expression is a unique feature of this form of histiocytosis, since it is absent in other histiocytic proliferations that we have studied, including Langerhans cell histiocytosis (10 cases), juvenile xanthogranuloma (8 cases solitary, 1 case systemic), familial hemophagocytic lymphohistiocytosis (3 cases), and Rosai-Dorfman disease (6 cases). Although presence of ALK gene translocation may suggest that ALK+ histiocytosis is a neoplastic disorder, we are cautious of this interpretation because of the favorable outcome in case 3 even without cytotoxic therapy, and in case 2, even though no further cytotoxic therapy was given for residual disease. Furthermore, the delayed clinical response to cytotoxic therapy in cases 1 and 2 renders it difficult to ascribe the response to chemotherapy versus natural resolution of disease.

In summary, ALK+ histiocytosis is a distinct form of histiocytic proliferative disorder that clinically may suggest a storage disorder. Based on this limited series, the disease tends to resolve slowly, but can be life threatening during the active phase.

Authorship

Contribution: J.K.C.C. and C.W.C. conceived the study, collected and analyzed the data, and drafted the paper; E.A., W.Y.W.T., K.C.L., and K.T. contributed patient materials and analyzed the data; and L.L. and G.D. performed special studies and analyzed the data.

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References

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Figure 1. Liver and skin biopsies. (A) Liver biopsy of case 2 shows infiltration of sinusoids by large histiocytes, which on causal examination are difficult to distinguish from the hepatocytes. (B) Liver biopsy of case 1 shows aggregates of histiocytes (arrows) in the sinusoids. The histiocytes have irregularly folded nuclei and abundant lightly eosinophilic cytoplasm. (C) Morphologic spectrum of proliferated histiocytes in the liver sinusoids. The histiocytes have 1 or 2 nuclei, which often show marked irregular foldings and small nucleoli. Some contain phagocyted blood cells, brown pigment, or fine vacuoles. (D) Skin lesion of case 1 shows dermal infiltrate of mononuclear cells and multinucleated giant cells; the latter showed wreathlike nuclei (upper panel). These cells are immunoreactive for ALK (lower panel). (E) The histiocytes in the sinusoids show positive immunostaining for CD163. (F) Immunostaining for ALK highlights the sinusoidal distribution of the histiocytes (left panel). Higher magnification shows cell membrane and weak cytoplasmic staining (right panel). Images were captured with Olympus DP71 camera mounted on an Olympus microscope model BX61 (Tokyo, Japan). The objectives used for capturing the images were as follow: (A) 20× objective; (B) 100× objective; (C) 100× objective; (D) 40× objective; (E) 60× objective; (F, left) 10× objective; (F, right) 60× objective. Images were acquired using Olympus DP Controller, and whitening of the background and cropping of the images were performed using Adobe Photoshop CS (Adobe Systems, San Jose, CA).


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