CASE REPORT

Secondary Sea-Blue Histiocytosis in a Patient with Transfusion Dependent HbE-Beta Thalassaemia and Osteosarcoma

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Received: 23 January 2015 / Accepted: 17 August 2015 / Published online: 29 August 2015
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Abstract Secondary sea-blue histiocytosis occurs more frequently than the primary form and occurs consequent to a wide range of metabolic and haematologic disorders including thalassaemia. We report an 18-year-old Chinese boy with transfusion-dependent HbE-beta thalassaemia who complained of pain and swelling at the left iliac crest region for 2 months duration. Physical examination revealed pallor with hepatosplenomegaly. Local examination revealed a huge swelling 12 cm × 12 cm in diameter, firm in consistency and tender. Histopathological examination of the mass revealed an osteosarcoma. His bone marrow aspirate showed numerous sea-blue histiocytes, the cytoplasm of which was closely packed with fine granules that stained blue with May–Grunwald–Giemsa. The nuclei were centrally located in some cells and displaced towards

the periphery in other cells. There was no malignant cell infiltration in the marrow. The case is reported due to the co-incidental dual pathology in our patient (HbE-beta thalassaemia and osteosarcoma) and the unusual bone marrow finding of numerous sea-blue histiocytes.

Keywords Secondary sea-blue histiocytosis · HbE-beta thalassaemia · Bone marrow aspirates · Special stains

Introduction

Sea-blue histiocytosis is a rare disorder characterized by the presence of atypical macrophages (sea-blue histiocytes) in the bone marrow (BM), liver, spleen and less frequently in the lymph nodes, tonsils and other organs [1]. Sea-blue histiocytes are lipid-laden macrophages varying from 20 to 60 µm in diameter with a single eccentric nucleus their cytoplasm is distended and closely packed with granules that stain a characteristic sea-blue or blue-green with Romanowsky stains [2].

Sea-blue histiocytosis is classified as either primary or secondary (acquired); most cases are secondary to inherited lipid metabolic diseases such as Niemann–Pick disease, Fabry’s disease and ceroid storage diseases [3]. In these diseases specific enzyme deficiencies may lead to accumulation of unsaturated, oxidated, polymerized lipids such as ceroids of lipofuscin, glycopospholipids and sphingomyelin in the cytoplasm of histiocytes in various organs [4]. Primary sea-blue histiocytosis syndrome is a rare chronic benign condition of unknown etiology manifested by significant accumulation of sea-blue histiocytes in multiple organs [5]. This syndrome was first described by Silverstein et al. in 1970 as a clinical entity characterised by impaired liver and lung function, hepatosplenomegaly,

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lymphadenopathy and thrombocytopenia associated with the presence of sea-blue histiocytes in the spleen and BM [6]. It may progress to cirrhosis and portal hypertension in 15 % of cases [7].

Sea-blue histiocytosis involving the BM is commonly seen as a secondary phenomenon in association with a variety of systemic, metabolic, or haematologic disorders. Haematological disorders reported to be associated with BM sea-blue histiocytosis are chronic myeloid leukaemia (CML), polycythaemia vera (PV), myelodysplastic syndrome (MDS), chronic immune thrombocytopenic purpura (ITP), sickle cell anaemia and thalassaemia [7]. With the exception of CML, the finding of sea-blue histiocytes in the BM is relatively rare [2]. This secondary phenomenon has also been observed in a few patients with systemic diseases such as sarcoidosis, chronic granulomatous disease, lipochrome histiocytosis, hyperlipoproteinaemia, and various lipidoses [8]. Additionally, secondary sea-blue histiocytosis occurs less frequently in prolonged intravenous nutrition with fat emulsions or sodium valproate administration [9]. When occurring in conjunction with storage disorders like Niemann Pick disease, it is important to be aware of the secondary nature of these cells to avoid misdiagnosis [10].

A review of literature reveals that secondary sea-blue histiocytosis has been previously described in association with β thalassaemia (homozygous and heterozygous) and HbE-beta thalassaemia [8, 11, 12]. In these disorders, it forms part of the spectrum of secondary histiocytoses including pseudo-Gaucher cells that arise as a consequence of increased erythroid cell turnover [13].

We report an interesting co-occurrence of hemoglobin disorder with a malignancy where the staging marrow revealed secondary sea-blue histiocytosis.

Case Report

An 18-year-old Chinese boy with transfusion dependent HbE-beta thalassaemia and chronic iron overload, on desferal 2.5 g subcutaneous infusion five times per week, presented with history of left lower back pain for 2 months. The pain was intermittent, worsened at night and radiated to the left hip but he was still able to ambulate. He also complained of swelling at the left iliac crest, progressively increasing in size for the past 2 weeks. There was no history of fever, loss of appetite, loss of weight or bowel or urinary incontinence. Physical examination revealed mild pallor and hepatosplenomegaly. The spleen and liver sizes below the costal margin were 12 and 10 cm, respectively. There was no lymphadenopathy. Local examination of the swelling revealed a huge mass of 12 cm $\times$ 12 cm in diameter, firm and tender. The mass was fixed to the

underlying bone with intact overlying skin, stretched but not reddened or ulcerated.

An X-ray of the pelvic bone showed aggressive sclerotic bony lesion at the left iliac wing with dense cloud-like calcification. Subsequently, a magnetic resonance imaging (MRI) pelvis showed a large expansile lobulated left iliac bone tumour with local infiltration, bony metastasis and regional lymphadenopathy suggestive of Ewing sarcoma with a differential diagnosis of osteosarcoma and chondrosarcoma. Histopathological examination of the tumour confirmed osteosarcoma. On further work up, he was found to have multiple metastatic lesions involving L1, L2 and L5 vertebrae, calcified lung, pleural bases lesions and multiple regional lymphadenopathy. The full blood count report revealed haemoglobin 8.2 g/dl, Hct 23.8 %, MCV 74.5 fl, MCH 25.6 pg, white cells count $12.4 \times 10^9/L$ and platelet $523 \times 10^9/L$. Peripheral blood smear showed presence of dimorphic red cells (normochromic and hypochromic red cells) with anisopoikilocytosis, spherocytosis and target red cells. There was no leukoerythroblastosis. The alkaline phosphatase (ALP) level was markedly raised (1576 U/L) and the serum lactate dehydrogenase (LDH) was also elevated (795 U/L). The staging BM aspirates showed erythroid hyperplasia with numerous atypical macrophages, with distended cytoplasm closely packed with fine granules that stained blue with May–Grunwald–Giemsa (MGG). The nuclei were centrally located in some cells and displaced towards the periphery in other cells. These findings were consistent with sea-blue histiocytosis (Fig. 1a). Perls stain showed positive iron in numerous histiocytes (Fig. 1b). Periodic acid–Schiff (PAS) also showed positivity in these cells (Fig. 1c), and they were negative with peroxidase stain. The trephine biopsy also showed erythroid hyperplasia with numerous foamy macrophages (Fig. 1d). There was no evidence of malignant infiltration. Ziehl Neelsen stain was negative in these cells.

Subsequently, he was started on systemic chemotherapy comprising of intravenous Doxorubicin, Cisplatin and Methotrexate (PAM protocol). He was given several courses of the chemotherapy in which he was refractory to and finally succumbed to his condition.

Discussion

Secondary sea-blue histiocytosis is an acquired lipidosis, in which inclusions of differing morphology, but probably all of lipid character accumulate in histiocytes [14]. In most haematological conditions, the disease is characterized by increased turnover of BM cells [2]. In these conditions the histiocytes may phagocytose erythrocytes, leukocytes, or platelets. Products of the ingested cells accumulate in the

cytoplasm of the histiocytes because of relative insufficiency of catabolic enzymes [15].

Rywlin et al. reported that ceroid-containing histiocytes were not diagnostic of any disease and may be found in the spleen and/or BM in different entities. The finding of sea-blue histiocytes in the BM should be followed by cytochemical studies to confirm the presence of ceroid [16]. Therefore, additional clinical data, laboratory and morphologic tests are necessary to establish a specific diagnosis. Parker et al. proposed that sea-blue histiocytes could be a marker for abnormalities of lipid metabolism [17].

In BM aspirates, sea-blue histiocytes stain blue or blue-green with Romanowsky stains [9]. Further, the histiocytes are orange reddish with PAS and black with Sudan black [4] and are sometimes positive for iron [9]. Whereas, in BM biopsy sea-blue histiocytes are brownish-yellow in H&E stained sections and blue with Giemsa stain [9]. Although their cytoplasmic contents are reported to be acid-fast [9], this was not observed in our case. They are also known to exhibit autofluorescence [9]. In our case we have confirmed the presence of sea-blue histiocytes by using the special stains such as Perls stain, Giemsa, and PAS. Hayhoe et al. studied the three varieties of compound lipid inclusions occurring as a secondary phenomenon in marrow macrophages (Birefringent blue crystals and Gaucher-like cells form one variety, sea-blue granules another, and grey-green crystals a third) by using Romanowsky staining, ultraviolet (UV) fluorescence, and polarised light. They described the sea-blue granules as small, rounded bodies of 1–3 μm diameter which stained with a varying degree of intensity a sea-blue color, their number ranging from a few to many in any affected histiocyte. Sea-blue inclusion material in UV light may show

a pink-colored autofluorescence but they have not found it to be birefringent. Electron microscope examination of sea-blue histiocytes revealed rounded osmiphilic inclusions occasionally displaying a finger print pattern [14].

In 1960, Gupta et al. demonstrated that the foamy appearance of the storage cells in the spleen in thalassaemia is due to accumulation of an acidic mucopolysaccharide of the chondroitin sulphuric acid type in the cytoplasm of the histiocytes. This mucopolysaccharide is liberated by the lysis of the abnormal erythroid cells in thalassaemia which then taken up by the histiocytes. This polysaccharide showed intense red coloration with PAS reaction as we had shown in our case [12]. Beltrami et al. reported that the histiocytes in thalassaemia have a distinctive morphology when visualized by electron microscope. They are filled with cytoplasmic inclusion bodies that contain fine fibrils arranged in parallel. These cells are probably derived from phagocytosis of erythrocytes and their precursors by histiocytes that unable to metabolize them completely. When stained by Giemsa method, they resemble those of the syndrome of the sea-blue histiocytes [15]. Quattrin et al. studied the relationship between sea-blue histiocytosis and β -thalassaemia genes in the same individual and they concluded that the two genes are most likely independent [11].

In conclusion, we report a rare condition of secondary sea-blue histiocytosis in a patient with transfusion dependent HbE-beta thalassaemia and iliac bone osteosarcoma. Although their recognition was straightforward in our case with the help of cytochemical stains, haematopathologists should be aware of the secondary nature of these cells and the numerous settings that they may arise in, to avoid diagnostic confusion.

Appendix

See Fig. 1.

Fig. 1 Bone marrow aspirate shows **a** sea-blue histiocytes with peripherally located nuclei and cytoplasm packed with fine granules staining blue with May–Grunwald–Giemsa (MGG) $\times 600$. **b** Hemosiderin-laden histiocytes (Perls stain, safranin counterstain, $\times 400$). **c** Periodic acid–Schiff stain positive histiocytes. One shows

phagocytosed normoblasts (*arrow*) (PAS stain, hematoxylin counterstain, $\times 400$). **d** Bone marrow trephine biopsy shows erythroid hyperplasia with presence of foamy macrophages (*arrows*), Hematoxylin and Eosin (H&E) $\times 400$

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