CASE REPORTS

Intrathoracic and Pelvic Extramedullary Haematopoiesis in Sickle Cell Disease

A Case Report

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ABSTRACT

Intrathoracic extramedullary haematopoiesis is a rare entity encountered in patients with long standing anaemias such as thalassaemia and congenital spherocytosis. It is rare in patients with homozygous sickle cell disease; only 11 cases of intrathoracic and two cases of pelvic extramedullary haematopoiesis have been documented in the literature. We report the case of a 30-year old man with homozygous sickle cell disease with intrathoracic and pelvic extramedullary haematopoiesis, the first case to be documented from the Caribbean.

La Hematopoyesis Extramedular Intratorácica y Pélvica en la Enfermedad de Células Falciformes

Reporte de un Caso

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RESUMEN

La hematopoyesis extramedular intratorácica es una entidad que raras veces se encuentra en pacientes con anemias de larga duración tales como la talasemia y la esferocitosis congénita. También es rara en pacientes que padecen la enfermedad de células falciformes homocigóticas. En la literatura se han documentado sólo 11 casos de hematopoyesis extramedular intratorácica y dos casos de hematopoyesis extramedular pélvica. Reportamos el caso de un hombre de 30 años de edad con la enfermedad de células falciformes homocigóticas con hematopoyesis extramedular intratorácica y pélvica – el primer caso que se documenta en el Caribe.

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INTRODUCTION

Extramedullary haematopoiesis (EMH) is a rare entity, typically found in patients with prolonged anaemias, such as haemolytic anaemias (including thalassaemias, congenital spherocytosis and sickle cell disease), myelofibrosis or myeloproliferative disorders and some neoplasms as a compensatory mechanism necessary to sustain sufficient erythrogenesis (1). Liver, spleen and lymph nodes are frequently involved. However, EMH may also develop in other sites such as the thymus, kidney and retroperitoneum (2). It is rarely encountered in the thorax (3) and extrathoracic locations are even less common (4). We report a case of thoracic and pelvic EMH in a Jamaican male with homozygous sickle cell (SS) disease. To the best of our knowledge, this is the first case to be documented in the English-speaking Caribbean.

CASE REPORT

This 30-year old Jamaican male with SS disease, who had been a part of the Jamaican Sickle Cell Cohort Study, was first diagnosed at neonatal screening and had been followed-up for all routine clinical care at the Sickle Cell Unit of the University of the West Indies. His steady state haematology showed haemoglobin 7.1 gm/dL, mean corpuscular volume 81fL, reticulocytes 13%, white blood cells 14 x 10^3/L, platelets 539 000 and fetal haemoglobin levels 1.8%. He had

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no α-thalassaemia and his β-haplotype was BEN/BEN x CAR.

Since early childhood, significant clinical events included multiple episodes of bony painful crises, acute chest syndromes, acute splenic sequestration and right cerebrovascular accident at age nine years without residual hemiparesis. Also in his childhood, he had blood transfusions on three occasions for acute events, such as acute splenic sequestration, acute chest syndrome with falling haemoglobin and an episode of salmonella sepsis. The Sickle Cell Unit in Jamaica does not offer chronic transfusions as a management strategy for severe sickle cell disease due to resource constraints. The unit has just begun to offer hydroxyurea therapy to adults with severe disease. This patient was never placed on either of these therapies.

In his adulthood, he developed chronic leg ulcers, stuttering priapism and unremitting bone pain for which he was prescribed oral analgesics such as pethidine and morphine repeatedly. He was diagnosed as having essential hypertension at age 26 years but was rarely compliant with the antihypertensive medications.

He presented to the Accident and Emergency Unit of the University Hospital of the West Indies in May 2006 with complaints of right upper abdominal and bilateral thigh pain of two days' duration. On examination, he was found to have an enlarged tender liver. On investigation, the haemoglobin was at 7.2 gm/dL and all other haematological, hepatic and renal parameters were within normal range. He refused admission, was treated with oral morphine and went home on oral analgesics. He was found dead at home a day later.

At post-mortem, the body was that of a asthenic young man of African descent with chronic leg ulcers and frontal bossing. Internal examination was remarkable for the presence of intrathoracic, paravertebral dark red-purple, fleshy, soft lobulated masses bilaterally at T4-T5 (Fig. 1). The right mass measured 7 x 5.5 x 3 cm and the left 6 x 5 x 3 cm. Masses, with similar appearance, ranging from 1 to 3 cm in diameter were also present along the sacrum. The thoracic masses appeared to be continuous with the bone marrow which was expanded (Fig. 2).

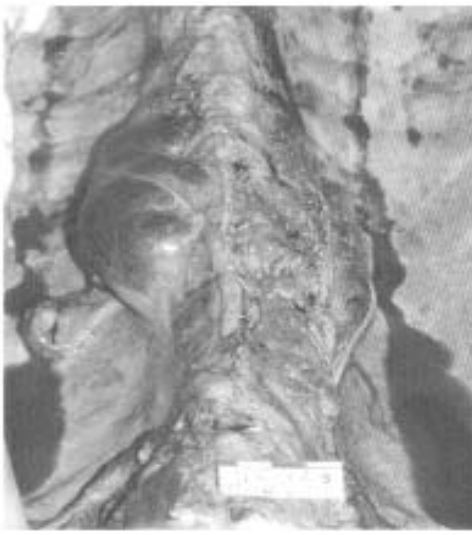

Fig. 1: Intrathoracic, paravertebral, bilateral masses of extramedullary haematopoiesis.

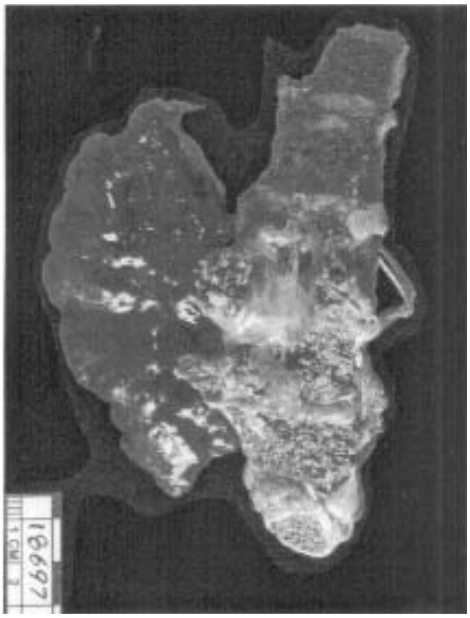

Fig. 2: The cut section of the thoracic vertebrae and the right-sided masses showing continuity with the expanded bone marrow in places.

The calvarium showed widening of the frontal bones with expansion of the marrow associated with spicule formation. The cross-section of the frontal bones measured 2.9 cm.

Histological examination of the paravertebral and the sacral masses showed extramedullary haematopoiesis with sheets of nucleated red blood cells and megakaryocytes (Fig. 3). No anatomical cause of death was identified. This was

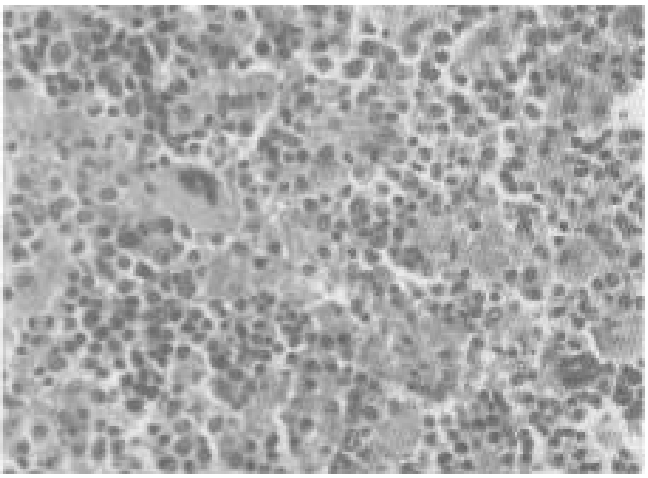

Fig. 3: Photomicrograph of the extramedullary haematopoiesis showing increased cellularity and scattered megakaryocytes.

not surprising as 9% of Jamaican patients with SS disease may not show any morphological evidence of the cause of death (5). The morphine and pethidine levels were not elevated in the blood samples taken at post-mortem.

In addition, there were stigmata of sickle cell disease and cardiomegaly (720 gm) with concentric left ventricular hypertrophy in keeping with essential hypertension and chronic anaemia.

DISCUSSION

Extramedullary haematopiesis refers to the presence of haematopoietic tissue in locations other than the bone marrow. It is observed in people suffering from prolonged severe anaemias and is a pathophysiological compensatory response necessary to sustain sufficient erythrogenesis in states of disturbed medullary haematopoiesis (1). It is encountered in some of the haemoglobinopathies such as thalassaemias, hereditary spherocytosis and sickle cell disease as well as in other disorders such as myelofibrosis, lymphomas and leukaemias (1). A rare case of EMH in alcohol-related macrocytosis was reported by De Geeter in 1996 (6).

Extramedullary haematopoiesis usually occurs in blood forming organs like liver, spleen and lymph nodes but is rarely seen in other locations such as middle ear, paranasal sinuses, epidural space, scalp, breast, prostate, epididymis, thymus, kidney, adrenal glands, thorax, pleura and pelvis (2, 4, 7–13). The foci seen in different organs are generally microscopic but rarely enlarged. Intrathoracic and pelvic EMH, though rare, are more commonly described in thalassaemias and hereditary spherocytosis and less commonly in sickle cell anaemia, both in homozygote and compound forms (7, 14). As far as could be determined, in homozygous SS disease, intrathoracic EMH has only been described in 11 cases (7, 10, 13, 15) and pelvic EMH in two cases (4, 8). The intrathoracic masses may be located bilaterally along the entire thoracic paravertebral areas or may be unilateral, mostly below the T6 level. In addition, they may be seen subpleurally, medial to the lateral portions of the ribs (7).

Several theories have been proposed to explain the pathogenesis of EMH. Firstly, it is likely that the bone marrow stem cells herniate through the thinned cortex of the vertebrae or ribs, perhaps abetted by the negative intrathoracic pressure (14). Lawson *et al* (16, 17) taking images of the specimens, confirmed the theory by showing the continuation of the paravertebral masses with the bone marrow. In contrast, the few autopsy cases of SS disease, sickle cell-β thalassaemias and hereditary spherocytosis have failed to show any continuity between the paravertebral masses or ribs and the bone marrow (15, 18). It is possible that continuity may have once existed and eventually got obliterated. In the index case, there was expansion of the bone marrow, thinning and erosion of the vertebral cortices (T4/T5) and the paravertebral masses appeared to be continuous in places with the hyperplastic bone marrow (Fig. 2).

Secondly, EMH may be due to a proliferation of heterotropic rests of stem cells or the multipotential cells which transform into nodules of haematopoietic tissue when needed (19, 20). Thirdly, it is also possible that the intrathoracic EMH is the result of embolization of haematopoietic tissue originating from other areas with EMH like the spleen (7, 14).

It is postulated that by suppressing the bone marrow either by blood transfusion or by increasing the level of HbF using hydroxyurea, there might be a reduction in the risk of EMH. Among adult patients with thalassaemia, the entity is more commonly reported with thalassaemia intermedia. This is because these patients reach adult life without the need for frequent blood transfusions as their haemoglobin levels remain higher than 7 gm/dL. In contrast, EMH occurs less commonly in thalassaemia major as hypertransfusion regimen is carried out regularly with these patients (21). The index patient received neither frequent blood transfusions nor hydroxyurea therapy.

Intrathoracic EMH is mostly located in the posterior mediastinum and tends to be asymptomatic. It is usually discovered incidentally on imaging. It may occasionally give symptoms such as chest pain, respiratory insufficiency, pleural effusion or haemothorax which may even be fatal (10, 14, 22). Elsewhere, these may present as abdominal and pelvic mass lesions (4, 23), hearing problems (11, 12, 24) or spinal cord compression with paraplegia (25, 26).

Extramedullary haematopoiesis can be diagnosed by radioimaging and fine needle aspiration. A typical radiographic appearance presents as unilateral or bilateral smooth, well circumscribed, lobulated paravertebral or paracostal masses (7, 10) without erosion of cortices, mostly located below T6. Occasionally, they can be seen along the entire length of the vertebral column. Computed tomography (CT) has been widely used (1, 7, 10, 22) but magnetic resonance imaging (MRI) is found to be superior (27). Computed tomography scans and MRI may reveal heterogeneous and homogeneous areas, depending upon the amount of fat within the mass (14). Pressure changes on the adjacent vertebrae or ribs are not seen. Older inactive masses may reveal iron deposition.

Fine needle aspiration cytology has been employed as a useful technique to provide definitive tissue diagnosis of EMH (13, 23). These masses tend to be slow growing and therefore should not be subjected to aggressive diagnostic and therapeutic measures, if asymptomatic (7). In symptomatic cases, they have been shown to regress with multiple blood transfusions (26) and hydroxyurea therapy (28). Those suffering from compressive symptoms respond to surgical decompression and/or low dose radiotherapy (25, 29).

In Jamaica, 10% of the population carries the sickle cell trait and 1 in 300 live births has SS disease (30). The patients are closely followed up and treated for their symptoms and complications in the Sickle Cell Unit at the Uni-

versity of the West Indies and the University Hospital of the West Indies. Autopsy is performed in nearly half of all cases dying with homozygous sickle cell disease (31). However, paravertebral and pelvic EMH has not been reported in Jamaica to date, either on radioimaging or on autopsies performed in cases with sickle cell diseases even though multiple blood transfusions and hydroxyurea therapy are not offered routinely to these patients. This is the first case of EMH associated with SS disease in a Jamaican patient. We report this entity in order to increase awareness that it may give mass lesions in SS disease and to avoid aggressive therapeutic measures in asymptomatic cases.

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REFERENCES

1. Murakami T, Dixon AC, Ho RC, Nakamura JM. Asymptomatic intrathoracic extramedullary hematopoiesis: a report of three cases. Hawaii Med J 1989; **48**: 430–2, 434–6.
2. Castelli R, Graziadei G, Karimi M, Cappellini MD. Intrathoracic masses due to extramedullary hematopoiesis. Am J Med Sci 2004; **328**: 299–303.
3. Kouraklis G, Dosios T. Intrathoracic extramedullary hematopoiesis simulating tumor, in a patient with sickle cell anemia. Eur J Cardiothorac Surg 1994; **8**: 220–1.
4. Sebes JI, Massie JD, White TJ, 3rd, Kraus AP. Pelvic extramedullary hematopoiesis. J Nucl Med 1984; **25**: 209–10.
5. Thomas AN, Pattison C, Serjeant GR. Causes of death in sickle-cell disease in Jamaica. Br Med J (Clin Res Ed) 1982; **285**: 633–5.
6. De Geeter F, Van Renterghem D. Scintigraphic diagnosis of intrathoracic extramedullary hematopoiesis in alcohol-related macrocytosis. J Nucl Med 1996; **37**: 473–5.
7. Gumbs RV, Higginbotham-Ford EA, Teal JS, Kletter GG, Castro O. Thoracic extramedullary hematopoiesis in sickle-cell disease. AJR Am J Roentgenol 1987; **149**: 889–93.
8. Lewkow LM, Shah I. Sickle cell anemia and epidural extramedullary hematopoiesis. Am J Med 1984; **76**: 748–51.
9. Joseph M, Rajshekhar V, Chandy MJ. Haematopoietic tissue presenting as a sphenoid sinus mass: case report. Neuroradiology 2000; **42**: 153–4.
10. Lall C, Payne DK. A patient with anemia and a paraspinal chest mass. Chest 2003; **124**: 732–4.
11. Applebaum EL, Frankel A. Extramedullary hematopoiesis of the middle ear. Am J Otolaryngol 1989; **10**: 287–90.
12. Giltman LI, Kavanagh KT, Babin RW, Crocker RA, Maijub AG, Black JN, Jr. Extramedullary hematopoiesis within the hypotympanicum presenting as a glomus tympanicum. Am J Otol 1986; **7**: 218–20.
13. Al-Marzooq YM, Al-Bahrani AT, Chopra R, Al-Momatten MI. Fine-needle aspiration biopsy diagnosis of intrathoracic extramedullary hematopoiesis presenting as a posterior mediastinal tumor in a patient with sickle-cell disease: Case report. Diagn Cytopathol 2004; **30**: 119–21.
14. Chute DJ, Fowler DR. Fatal hemothorax due to rupture of an intrathoracic extramedullary hematopoietic nodule. Am J Forensic Med Pathol 2004; **25**: 74–7.
15. Seidler RC, Becker JA. Intrathoracic extramedullary hematopoiesis. Radiology 1964; **83**: 1057–9.
16. Lawson JP, Ablow RC, Pearson HA. The ribs in thalassemia. II. The pathogenesis of the changes. Radiology 1981; **140**: 673–9.
17. Lawson JP, Ablow RC, Pearson HA. The ribs in thalassemia. I. The relationship to therapy. Radiology 1981; **140**: 663–72.
18. Verani R, Olson J, Moake JL. Intrathoracic extramedullary hematopoiesis: report of a case in a patient with sickle-cell disease-beta-thalassemia. Am J Clin Pathol 1980; **73**: 133–7.
19. Tsitouridis J, Stamos S, Hassapopoulou E, Tsitouridis K, Nikolopoulos P. Extramedullary paraspinal hematopoiesis in thalassemia: CT and MRI evaluation. Eur J Radiol 1999; **30**: 33–8.
20. Alorainy IA, Al-Asmi AR, del Carpio R. MRI features of epidural extramedullary hematopoiesis. Eur J Radiol 2000; **35**: 8–11.
21. Korsten J, Grossman H, Winchester PH, Canale VC. Extramedullary hematopoiesis in patients with thalassemia anemia. Radiology 1970; **95**: 257–63.
22. Chu KA, Lai RS, Lee CH, Lu JY, Chang HC, Chiang HT. Intrathoracic extramedullary haematopoiesis complicated by massive haemothorax in alpha-thalassaemia. Thorax 1999; **54**: 466–8.
23. Tamiolakis D, PTassopoulos P, Simopoulos C, Kotini A, Venizelos J, Alexiadis G et al. Renal extramedullary hematopoietic tumor diagnosed by fine needle aspiration: a case report. Acta Clin Belg 2003; **58**: 299–301.
24. Aronsohn MS, Antonelli PJ, Mancuso A. Extramedullary hematopoiesis presenting as a middle ear mass. Otol Neurotol 2003; **24**: 963–4.
25. Abbassioun K, Amir-Jamshidi A. Curable paraplegia due to extradural hematopoietic tissue in thalassemia. Neurosurgery 1982; **11**: 804–7.
26. Aliberti B, Patrikiou A, Terentiou A, Frangatou S, Papadimitriou A. Spinal cord compression due to extramedullary haematopoiesis in two patients with thalassaemia: complete regression with blood transfusion therapy. J Neurol 2001; **248**: 18–22.
27. Papavasiliou C, Gouliamos A, Vlahos L, Trakadas S, Kalovidouris A, Pouliades G. CT and MRI of symptomatic spinal involvement by extramedullary haemopoiesis. Clin Radiol 1990; **42**: 91–2.
28. Saxon BR, Rees D, Olivieri NF. Regression of extramedullary haemopoiesis and augmentation of fetal haemoglobin concentration during hydroxyurea therapy in beta thalassaemia. Br J Haematol 1998; **101**: 416–9.
29. Singhal S, Sharma S, Dixit S, De S, Chander S, Rath GK et al. The role of radiation therapy in the management of spinal cord compression due to extramedullary haematopoiesis in thalassaemia. J Neurol Neurosurg Psychiatry 1992; **55**: 310–2.
30. Serjeant GR, Serjeant BE. Sickle Cell Disease. Third ed. Oxford: Oxford University Press; 2001.
31. Wierenga K, Hambleton I, Grandison T, Char G. Mortality and circumstances of death in Jamaican patients with homozygous sickle cell disease. 24th Annual Meeting of the National Sickle Cell Disease Program; 2000; Philadelphia, Pennsylvania; 2000.