Diabetes insipidus complicating myelofibrosis

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Summary: A 68 year old man developed cranial diabetes insipidus 3 years after the diagnosis of myelofibrosis, coincident with a marked increase in nucleated cell count. No mass lesion was demonstrable on computed tomographic or magnetic resonance imaging. It is suggested that hypothalamic damage was caused by local infiltration or infarction, a complication of myelofibrosis which has not previously been reported.

Introduction

Acute or chronic leukaemia is a recognized cause of cranial diabetes insipidus (DI) accounting for 1–2% of cases.^{1,2} DI has only once been described as a complication of myelofibrosis when it was caused by hypothalamic and posterior pituitary compression by extra-medullary haematopoietic tissue.³ We report a second case in which there was no evidence of extrinsic hypothalamic compression and suggest, by analogy with leukaemia,⁴ that DI was caused by direct hypothalamic involvement.

Case report

A 68 year old retired farmer was found in January 1983 to have hepatosplenomegaly; the haemoglobin concentration was 7.0 g/dl, total nucleated cell count $11.9 \times 10^9/l$, platelet count $223 \times 10^9/l$ and the film leucoerythroblastic. Trephine biopsy showed a hypercellular marrow with increased megakaryocytes and a marked increase in reticulin, consistent with myelofibrosis. Over the next 10 months he needed blood transfusions totalling 40 units so a splenectomy was performed. Histology of the spleen showed myeloid metaplasia. He received 30 units of blood over the next year after which his haemoglobin stabilized at 10 g/dl without transfusion and he remained well for two further years (Figure 1).

Between June and October 1986, his total nucleated cell count rose from 20 to $134 \times 10^9/l$ (neutrophils 24, myelocytes 50, metamyelocytes 29, nucleated reds 15, lymphocytes 9, monocytes $7 \times 10^9/l$). Simultaneously, the platelet count rose and haemoglobin fell to 7.5 g/dl.

He was started on hydroxyurea and allopurinol, despite which he needed regular blood transfusions. At this time (and before starting hydroxyurea) he complained of polydipsia and thirst with a 24 hour urine volume of 6.2 litres. The diagnosis of DI was confirmed by a 7 hour water deprivation test during which serum osmolality rose from 313 to 332 mosm/kg (reference range 280–300 mosm/kg) with a peak urine osmolality of 228 mosm/kg and average urine volume of 280 ml/h. There was an immediate symptomatic and biochemical response to desmopressin. Twelve months later, he remained dependent on intranasal desmopressin, continued hydroxyurea and required blood transfusions but was otherwise well. Bone marrow histology remained consistent with myelofibrosis and chromosomes were normal. Visual fields and acuities were normal and there were no focal neurological signs or evidence of raised intracranial pressure.

High resolution pituitary-dedicated computed tomographic (CT) scan showed a pituitary gland of normal size but low attenuation. The hypothalamus was normal and there was no mass lesion. Magnetic resonance (MR) imaging showed no abnormality of the pituitary or hypothalamus. Other investigations showed that the serum testosterone was at the lower end of the reference range but luteinizing hormones rose appropriately to gonadotrophin releasing hormone (100 µg intravenous bolus) and there was no other evidence of anterior pituitary insufficiency. Serum ferritin was 2996 µg/l (reference range 6–224) indicating significant tissue iron-loading.

Discussion

The patient developed cranial DI three and a half years after the diagnosis of myelofibrosis. The association

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Figure 1 Flow chart from diagnosis of haematological measures and other events.

was unlikely to be coincidental since cranial DI is nearly always secondary to disease of the hypothalamus in older patients.² Despite similarities in the history, our case differed from that of Badon *et al.*³ because a mass lesion was excluded by high resolution CT and MR imaging. Iron deposition due to multiple transfusions might be considered a possible cause. Pituitary siderosis has been described⁵ but both the histological changes and functional impairment preferentially affect the anterior lobe. Another possibility is direct hypothalamo-pituitary involvement in the disease process.

Although rare,⁶ DI has been described in all types of acute leukaemia⁴ and may be their presenting feature.^{7,8} It has also been described in chronic myeloid leukaemia, often at the time of acute blastic transformation.^{4,9} Two pathological appearances have been reported: diffuse leukaemic infiltration and leukostasis with infarction, haemorrhage and coagulative necrosis.^{4,10} Spontaneous recovery or improvement fol-

lowing chemotherapy or radiotherapy have not been reported. In some cases, the response to antidiuretic hormone and desmopressin is poor, probably due to leukaemic renal tubular involvement.¹¹ Why the disease selectively involves the supra-optic and paraventricular nuclei and spares the anterior pituitary and remainder of the central nervous system is unknown.

We confirm that DI may complicate myelofibrosis. The exact mechanism could not be demonstrated in our patient but the coincidence between a sharp rise in white cell count and the onset of DI suggests that local infiltration or infarction may have been responsible.

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