Clinical Reports

Histiocytosis X involving the thyroid and hypothalamus

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Summary: A case of histiocytosis X involving the thyroid and hypothalamus is reported. A 16 year old female presented with amenorrhoea and diabetes insipidus. She subsequently developed a painful goitre with biochemical hypothyroidism, and stridor. The stridor and goitre responded to cyclophosphamide. Previous publications on the use of cytotoxics in histiocytosis X involving the thyroid are reviewed. We describe for the first time both the ultrasound appearances of the thyroid in this condition and the use of serial volumetric measurements to monitor therapy.

Introduction

Histiocytosis X involving the thyroid is rare. We report a patient who developed a subacute painful goitre with stridor and responded well to chemotherapy.

Case report

A 16 year old female presented with 2-year history of secondary amenorrhoea, polydipsia, polyuria and a substantial increase in body weight. Throughout this time she suffered from occipital headaches. Her menarche occurred at the age of 13 and after 2 cycles her menses ceased completely. Clinically she was overweight (weight 61 kg; height 154.5 cm). Pubic hair was absent and her skin was sallow. There was no galactorrhoea, visual fields were normal and at this time there was no goitre.

Investigations confirmed cranial diabetes insipidus and partial hypopituitarism. Serum growth hormone was undetectable with no response to glucagon challenge (1 mg subcutaneously) and the cortisol value rose suboptimally from a low basal level of 53 nmol/l to 259 nmol/l. The serum prolactin was mildly elevated at 970 IU/l (normal: 870 IU/l). Serum oestrogen was undetectable. Luteinizing hormone (LH) remained less than 1.8 IU/l and follicle stimulating hormone (FSH) rose from 0.8 only to 1.3 IU/l when 100 µg of LH releasing hormone (LHRH) was given intra-

venously, confirming hypogonadotrophic hypogonadism. Thyroid function was initially normal with a basal sensitive thyroid stimulating hormone (sTSH) of 0.8 IU/l rising to 7.1 mIU/l (normal 0.3–4.0 mIU/l) after stimulation with 200 µg of thyrotrophin releasing hormone (TRH). Free thyroxine (T4) was 14.1 pmol/l (normal 7–21.8 pmol/l). Tumour markers, including alpha fetoprotein, human chorionic gonadotrophin and vanillylmandelic acid, were negative. Computed tomography (CT) demonstrated an enhancing soft tissue mass without calcification above the pituitary gland (Figure 1). Carotid angiography was normal.

Figure 1 An axial contrast enhanced CT scan across the supra-sella cistern demonstrates a markedly enhancing soft tissue mass (M) in the cistern above the pituitary fossa. P = pons, M.C.A. = middle cerebral artery.

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She was treated with intranasal desmopressin and hydrocortisone replacement therapy. Four months later she complained of flu-like symptoms associated with a sore throat and a painful tender goitre. Clinically she was euthyroid. Her ESR was elevated at 62 mm/h with a mild leucocytosis of $10.1 \times 10^9/l$. She had compensated primary hypothyroidism biochemically with an elevated sensitive TSH of 11.5 mIU/l (normal 0.3–4.0 mIU/l) and normal free triiodothyronine (T3) of 5.1 pmol/l (normal 2.2–6.3 pmol/l). Thyroid auto-antibodies and viral titre were negative. Ultrasound examination of her thyroid was grossly abnormal with coarse bright echoes on a diffusely dark gland (Figure 2). This was interpreted as being compatible with subacute thyroiditis. Despite initial improvement with a non-steroidal anti-inflammatory drug, she noticed increasing exertional dyspnoea and noisy breathing.

A cytological diagnosis of histiocytosis X was made by fine needle aspiration of the thyroid. A core biopsy for histology confirmed histiocytosis X with infiltration of the thyroid gland (Figure 3). S100 stain was positive and Birbeck granules were seen on electron microscopy. Staining for thyroglobulin was negative.

Her stridor and exertional dyspnoea progressively worsened, hepatomegaly developed, and hyperphagia with further weight gain were observed. A liver biopsy was refused. The sTSH rose further to 12.4 mIU/l with a low free T4 of 6.7 pmol/l (normal 7–21.8 pmol/l). Her haematological picture remained normal. Apart from mild elevation of transaminase, liver function tests were unremarkable. Immunoglobulin class, lymphocyte subset profile and T cell function were normal. The OKT4/OKT8 ratio was 1.52 (normal 0.9–2.7). A chest radiograph did not show any pulmonary infiltration but did demonstrate a narrow trachea. An ultrasound of her liver was compatible with

Figure 2 A transverse ultrasound scan across the thyroid gland (T). The thyroid is enlarged and has an abnormally bright texture on a dark background.

Figure 3 Histiocytosis X with thyroid involvement: an extensive infiltration of the thyroid gland by histiocytic-like cells characterised by an irregular nucleus, often exhibiting convolution and groove (arrow) and an ample eosinophilic cytoplasm. Only residual thyroid follicles are present (*). Haematoxyphil and eosin stain, $\times 320$.

fatty changes. Lung function studies demonstrated an obstructive defect and a flow volume loop showed the site of obstruction to be extrathoracic.

Her thyroid volume was measured by a modified version of previously published methodology.¹ The weight of a piece of standard tracing paper (10 cm $\times$ 10 cm $\times$ 0.5 cm) was obtained (W1); using sequential 'B' mode ultrasound scans at 0.5 cm intervals, the outline of the thyroid was traced on to paper and the cut sections of paper weighed (W2). The volume of the cut section is then calculated by the equation

$$\frac{W2 \times 50}{W1}$$

In view of the progression of disease with tracheal compression, prednisolone 60 mg daily and thyroxine replacement therapy were given. After 4 weeks of prednisolone there was no improvement, and cyclophosphamide, 1 g intravenously for 3 courses, was then given. On this treatment her stridor cleared, her flow volume loop returned to normal and the thyroid volume showed a marked reduction from 78.2 cm³ before treatment to 53.9 cm³ after treatment.

Discussion

Histiocytosis X is a group of clinical syndromes characterized by the primary proliferation of Langerhans cells.² The disease is rare, occurring in about 0.5/100,000 children in the USA.³ The most common endocrine involvement results in diabetes insipidus and growth hormone deficiency.² Clinical involvement of the thyroid is rare.^{4–12} In a review of the 10 cases now reported in English language

publications the ages of the patients range from 27 months to 28 years with slightly more males than females (6:4). All patients had a goitre and 4 of the patients were biochemically hypothyroid. This is the first reported case of a presentation resembling thyroiditis and it is interesting that the ultrasound features also resemble thyroiditis.¹³ Many of the patients (80%) also had diabetes insipidus which is a higher proportion than the 20–50% generally reported in histiocytosis X.¹⁴ Most also had growth hormone deficiency, and hypogonadism is reported in 3 patients. The site of the central endocrine lesion can be demonstrated histologically and biochemically to be in the hypothalamus, stalk, or posterior pituitary.⁶ In the patient detailed here the hyperphagia, diabetes insipidus, elevated serum prolactin and CT findings indicate a hypothalamic lesion. More general systemic disease is found in 6 of the 10 patients with involvement of bone, skin, lungs, ears, lymph nodes and liver. Liver involvement in our patient cannot be excluded in the absence of a liver biopsy, although ultrasound suggested a fatty liver.

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ing respiratory embarrassment has been documented only once before when it led to acute respiratory arrest in a child.¹¹ Treatment on that occasion was partial thyroidectomy followed by chemotherapy. The role of chemotherapy in histiocytosis X is controversial.² Whilst some feel it explains the improved life expectancy of patients with systemic involvement that has been documented since the introduction of chemotherapy, there have been no trials large enough to confirm the benefit of a specific regime. Chemotherapy has been used in 5 previous patients with thyroid involvement. All regimes have been different and include nitrogen mustard and prednisolone,⁴ vinblastine,⁹ vinblastine and prednisolone,⁸ 6-mercaptopurine and prednisolone,¹¹ and vincristine with adriamycin, CCNU and prednisolone.¹⁰ All have shown clinical improvement. Our decision to institute chemotherapy was on the basis of progressive disease and stridor. Clinically the stridor improved and, using both flow volume loops and a novel measurement of thyroid volume with sequential ultrasound measurements, we have documented a definite response to chemotherapy.

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