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Clearance of acanthosis nigricans associated with the HAIR-AN syndrome after partial pancreatectomy: an 11-year follow-up

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Summary

We describe a woman with the syndrome characterised by hyperandrogenism, insulin resistance and acanthosis nigricans (the HAIR-AN syndrome), and an associated insulinoma (islet B-cell tumour), whose signs and symptoms cleared after partial pancreatectomy.

Keywords: acanthosis nigricans; insulinoma; HAIR-AN syndrome; hyperinsulinaemia

In 1986, an obese 16-year-old white woman presented with drowsiness, lethargy, and headaches of one year's duration. She had had a mumps-like illness with parotid gland enlargement, amenorrhoea for 3 months (having previously had regular periods), and often felt thirsty. Her weight had increased by 13 kg to 122 kg (height 1.75 m). She had facial acne, sweaty palms, multiple abdominal striae, hirsutism on the arms and legs, a deep voice, and clitoromegaly. The neck, abdomen and axillae showed acanthosis nigricans (figure 1).¹ Her blood pressure was 160/100 mmHg with a regular pulse of 100 beats/min. Neurological examination was normal. Her haemoglobin was 17.0 g/dl and erythrocyte sedimentation rate was 52 mm in the first hour. A prolonged glucose tolerance test showed hypoglycaemia with a hyperinsulinaemic state. Other endocrine tests showed follicle-stimulating hormone (FSH) 33 IU/l (normal), luteinising hormone (LH) 25 IU/l (normal), LH:FSH ratio < 3 (>3 suggests polycystic ovarian disease), plasma testosterone 3.2, 7.1 and 9.3 nmol/l at monthly intervals (normal 0.2–3.0: slightly increased, consistent with obesity), and androstenedione 15 nmol/l (normal <10.2: not high enough to suggest an androgen-secretion tumour). Pelvic ultrasound scan was normal. Serum prolactin, triiodothyronine, thyroxine, thyroid-stimulating hormone, and thyroid-releasing hormone were normal. Urinary free cortisol was 355 nmol/24 h (normal), plasma cortisol 236 nmol/l at 09.00 am (normal) and 584 nmol/l at midnight (normal <150). Adrenocorticotropin was <10 ng/l (normal).

A diagnosis of HAIR-AN syndrome, characterised by hyperandrogenism, insulin resistance and acanthosis nigricans, was made and she was treated with dietary restriction to 800 kcal daily, and oral diazoxide, cyproterone acetate and ethinyloestradiol. In 1987, a diagnosis of insulinoma (islet cell hyperplasia) was made after extremely high serum levels of C-peptide were recorded: 3645 pmol/l basal (normal <1324), increasing to 11 590 pmol/l at 2 hours on a prolonged glucose tolerance test; serum insulin was 697 pmol/l and 2426 pmol/l, respectively (normal <50). The patient was insulin-resistant, but anti-insulin receptor antibodies were not detected. A distal hemipancreatectomy with splenectomy was performed in 1988, and her hypoglycaemia ceased. In 1989, she developed torsion of the left ovary, treated by salpingo-oophorectomy. Perioperative findings excluded polycystic ovaries. In 1990, after recurrent pulmonary emboli, warfarin was commenced.

Figure 1 Acanthosis nigricans of the left axilla in 1986

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Figure 2 The left axilla in 1997; acanthosis nigricans has virtually cleared

In 1995, her usually high requirement for insulin (typically 146 IU daily) dropped dramatically to 30 IU daily, and she experienced occasional hypoglycaemic episodes. A recurrence of the insulinoma could not be established, even though the C-peptide level was elevated at 2085 pmol/l. A short period without insulin, with dietary restriction only, resulted in recurrent hyperglycaemia and insulin was reinstated, the current dose being 20 IU bid.

In 1989, 3 years after her initial presentation and one year after hemipancreatectomy, the signs of virilism had regressed. She was not hirsute, the clitoral enlargement had regressed and her periods was normal. In 1997, 11 years after initial presentation, the acanthosis nigricans had virtually cleared (figure 2).

Summary points

- insulin may act as a growth factor to the skin leading to acanthosis nigricans when there is hyperinsulinaemia
- acanthosis nigricans may remit if high insulin levels, insulin resistance and insulin-binding defect are effectively treated

Discussion

Acanthosis nigricans has been associated with obesity, often with insulin resistance.¹ The resistance to insulin may result in hyperinsulinaemia and a down-regulation of insulin receptors to prevent hypoglycaemia.² Large amounts of unbound insulin are free to bind to insulin-like growth factor 1 (IGF-1) receptors.³ The binding of insulin to IGF-receptors on keratinocytes or fibroblasts leads to proliferation of the epidermis.³ This is clinically manifest as acanthosis nigricans, a cutaneous marker for tissue resistance to insulin with insulinaemia.¹⁻³ IGF receptors are also present in the ovarian stroma and, when bound by insulin, increased androgen production occurs, causing hirsutism and virilism.⁴

Only 1–3% of women with hyperandrogenism have been reported to show insulin resistance and acanthosis nigricans.⁵ This syndrome is probably underdiagnosed, as hyperandrogenetic women are not regularly screened for insulin resistance and acanthosis nigricans.¹ Our case shows that acanthosis nigricans and signs of virilism can remit if insulin levels, insulin resistance, and the insulin-binding defect are effectively treated. Spontaneous remission of the HAIR-AN syndrome has rarely been observed, although occasionally acanthosis nigricans associated with obesity can remit with weight reduction.¹

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Conjunctival MALT lymphoma: an unusual cause of red eye

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Summary

We describe a patient presenting with a red eye who was found to have conjunctival non-Hodgkin's lymphoma of the mucosa-associated lymphoid tissue (MALT) type.

Keywords: conjunctiva; lymphoma; MALT; red eye

A 79-year-old man presented with a 3-week history of a painless, red left eye. There was no discharge and minimal irritation. The vision in his left eye had deteriorated over several months secondary to cataract. His ophthalmic history included right cataract surgery one year previously. There was no relevant medical history.

On examination, right visual acuity was 6/9 and left was 6/18. He was found to have an infected left eye with an enlarged left caruncle and a fleshy 'salmon-pink' swelling that extended into the inferior forniceal conjunctiva (figure 1). The remainder of the ocular examination revealed a left cataract but no other abnormalities. There was no preauricular or submandibular lymphadenopathy and general examination confirmed localised disease. A biopsy of the inferior conjunctiva was performed.

Orbital computed tomography (CT) scans showed a soft tissue swelling anterior to the left globe. Conjunctival biopsy revealed a lymphoid infiltrate of the connective tissue and epithelium (figure 2). Immunostaining showed predominantly B cells with small numbers of T cells. This was consistent with a diagnosis of low grade non-Hodgkin's lymphoma of the MALT type (mucosa-associated lymphoid tissue). Blood tests including bone profile, serum immunoglobulins, marrow biopsy and

Figure 2 Biopsy specimen showing conjunctival epithelium and underlying stroma infiltrated by small lymphoid cells. Haematoxylin & eosin; orig magnification x 100

CT scans of head, neck, chest, abdomen and pelvis confirmed that the disease was localised.

He was referred to the radiotherapists for treatment. He was reviewed in the eye clinic 3 months later and found to have new conjunctival lesions in the right eye. A second biopsy of the right inferior forniceal conjunctiva showed a focal infiltrate of B and T cells with lymphoepithelial lesions consistent with the working diagnosis.

In view of the multifocal nature of his disease chemotherapy was commenced with oral chlorambucil. After six courses his lesions improved and the conjunctival infection resolved. He remains under regular review.

Discussion

In the early 1980s the term MALT was coined in order to describe a characteristic arrangement of lymphoid tissue found in certain mucosal surfaces.¹ Mucosa-associated lymphoid tissue is now recognised as giving rise to a specific form of tumour with distinct features, distinguishing MALT lymphoma from other forms of primary, non-Hodgkin's, extranodal lymphoma.^{2,3}

The commonest site of MALT in humans is the gastrointestinal tract, specifically stomach, terminal ileum and appendix.² It has also been described in the bronchus, salivary, thyroid and thymus glands. It was described in the conjunctiva in 1980 by Knowles and Jakobiec.³ Lymphoid tumours of the conjunctiva can pose problems in diagnosis since there is considerable overlap between benign and malignant lesions. Under normal circumstances the conjunctiva contains small numbers of

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Figure 1 Photograph of the left eye showing a fleshy, 'salmon-pink' lesion arising from the caruncle