An interesting case of thirst and polyuria

Q1: What are the possible causes of thirst and polyuria in this woman?
The two likely causes of thirst and polyuria in this patient are central diabetes insipidus secondary to previous pituitary surgery and hypercalcaemia. In our patient, a normal water deprivation test excluded central diabetes insipidus.

Cranial surgery accounts for 20% cases of central diabetes insipidus in adults. After pituitary surgery, persistent polyuria develops only if the injury is sufficiently high in the supraopticohypophyseal tract to cause degeneration of the supraoptic and paraventricular nucleus. Thus, although transient diabetes insipidus may follow any injury to the neurohypophysis, permanent cranial diabetes insipidus is uncommon after pituitary surgery.

Hypercalcaemia causes transient nephrogenic diabetes insipidus. Nephrogenic diabetes insipidus is manifested predominantly as a defect in maximum renal concentrating ability accompanied by a reduction in glomerular filtration rate. Other factors may include reduction in medullary solute content and inhibition of calcium by adenylate cyclase activation by arginine vasopressin in hormone sensitive epithelia.

Q2: What are the possible causes of hypercalcaemia?
The possible causes of hypercalcaemia include thyroid toxicosis, relative glucocorticoid insufficiency during illness and stress, dehydration, acromegaly, and hyperparathyroidism as part of multiple endocrine neoplasia syndromes.

Serum calcium concentrations are generally less than 2.7 mmol/l, but concentrations are reported very rarely in the literature and pre-replacement therapy after hypopituitarism.

Growth hormone stimulation of renal 1,25-dihydroxycholecalciferol concentrations, and hypercalcaemia. Serum calcium concentrations are generally less than 2.7 mmol/l, but life threatening hypercalcaemia has been described. Thyroid hormones absorb bone directly, although indirect resorption may also occur by activation of local factors such as interleukin-1 or by increasing sensitivity to circulating PTH. B-adrenergic blocking agents can reverse the hypercalcaemia as can definitive therapy with carbimazole.

Hypercalcaemia is detected in 6% cases of primary adrenal insufficiency but it is less common in secondary hypoadrenalism. Raised calcium binding proteins cause by haemocentration are a factor, but volume repletion with saline does not restore calcium concentrations to normal, for which glucocorticoid replacement is required.

Growth hormone stimulation of renal 1,25-dihydroxycholecalciferol concentrations result in increased intestinal calcium absorption and hypercalcaemia. Hypercalcaemia is uncommon in the absence of associated hyperparathyroidism and has been reported in none to 10% of cases in various series of patients with acromegaly.

In this patient the hypercalcaemia was due to thyrotoxicosis and glucocorticoid deficiency. It responded partially to replacement with isotonic saline and intravenous hydrocortisone and normalised completely after hyperthyroidism was treated with propranolol and carbimazole.

Q3: What is the cause of her thyrotoxicosis?
Her thyrotoxicosis is due to Graves’ disease as proved by homogenously increased tracer uptake on 131I thyroid uptake scan (fig 1; see p 248) and positive TSHRAb.

TSHRAb binds to the thyroid stimulating hormone receptor, activates adenylate cyclase, and increases intracellular cyclic AMP production and secretion. The TSHRAb in Graves’ disease is referred to as stimulating or agonist type TSHRAb, while various antibodies including a blocking TSHRAb may also be present. The non-blocking antibody may be coincident with the stimulating antibody. TSHRAb are not detectable in the normal population. A total of 80% to 100% of untreated hyperthyroid patients with Graves’ disease have detectable TSHRAb with thyroid stimulating activity.

Q4: Is there an association between acromegaly and thyrotoxicosis?
Acromegaly is well known to be associated with goitre at presentation of generalised acromegaly. In a series of 80 patients with acromegaly from an iodine deficient region, 71% had goitre compared with 35% in patients with prolactinomas. Goitres were more common in female acromegalic patients compared with males. Hyperthyroidism was noted in 5% cases and none were due to Graves’ disease.

Graves’ disease in patients with active or previous acromegaly has been reported very rarely in the literature and presented an unusual diagnostic challenge in this case, specially as she was on thyroxine replacement therapy after hypopituitarism.

Final diagnosis
Thyrotoxicosis due to Graves’ disease causing hypercalcaemia in a patient with hypopituitarism after treatment of acromegaly.

References

A proliferating pimple

Q1: What is the differential diagnosis on clinical examination?
The possible differential diagnosis on clinical examination is:
- Dermatofibroma.
- Psoric granuloma.
- Malignant melanoma.
- Metastatic oat cell carcinoma.
- Angiosarcoma.

Q2: What does the histology reveal (see p 249) and what histological techniques are used to establish the diagnosis?
The histology reveals malignant round cells consistent with a Merkel cell carcinoma or trabecular carcinoma. This is a rare primary neopendocrine tumour arising from Merkel cells.

History
The Merkel cell is a round cell in the basal layer of the epidermis named after Frederick Sigmund Merkel who discovered it in 1875. These round cells may be isolated or arranged in clusters around hair follicles, which are innervated and function as touch receptors. The tumour was first described by Yoker in 1972 who, along with Tang in 1978, described the intracytoplasmic dense core similar to those seen in neuroendocrine cells.

Q3: Discuss the clinical features and management of this lesion
Clinical features
The Merkel cell carcinoma is a rare but aggressive tumour presenting as a dark red to dark blue papule. It usually arises on the head, neck, and the extremities of the elderly. It is often associated with other neoplasms, most commonly with a squamous cell carcinoma previously resected from the same anatomical site. The two may also coexist. It is also associated with Bowen’s disease and basal cell carcinoma.

The most important differential diagnosis is metastatic oat cell carcinoma as there are no specific histological differentiating features between the two. It is, therefore, important to undertake a careful history and examination followed by chest radiography to rule out a primary lung lesion. The tumour has a high incidence of local recurrence (39%) and regional recurrence (46%). Distant metastasis occur to bones, liver, and lung.

Histology
The cellular pattern ranges from trabecular to an insular or to a diffuse growth but all may coexist in a single tumour. The lesion tends to occupy the whole of the dermis with sparing of epidermis by a thin zone of Grenz. Cytologically the cells are monomorphous with scanty cytoplasm and homogenous nuclei with a central nucleus (fig 1A). They may show a moulding effect as seen in small cell carcinomas.

Staining techniques
Silver stains are negative, indicating the small number of neurosecretory granules.

Immunohistochemistry
This is helpful in differentiating Merkel cell carcinoma from other tumours such as lymphoma, melanoma, and metastatic oat cell carcinoma.

The useful markers studies are:
- Positive for low molecular weight keratins such as AE1 or CAM 5.2, epithelial membrane antigen, neuron specific enolase (fig 1B), and chromagranin.
• Negative for S-100 protein, carcinoembryonic antigen, and lymphocytic markers.

Management

Some Merkel cell carcinomas have been reported to regress spontaneously.1 The optimal treatment is not well defined due to its rarity and the limitations of retrospective data.1 Early lesions can be managed by surgical resection alone. Mohs' microsurgery, which involves immediate histological assessment of resection margins, has a role in ensuring tumour clearance at the lateral and deep margins. It is not known whether prophylactic lymph node dissection and/or adjuvant radiotherapy increases the survival rate of about 1 cm a day, and may leave a similarly patterned scale in its wake. It is not raised, and is associated with pruritus (50%) and cosinophilia.

An episodic eruption

Q1: What is the name given to this rash (see p 249), and how is the appearance described?
The rash is erythema gyratum repens. The specific features of this figurate rash are concentric erythematous arcs and rings, as well as serpiginous bands and stripes in alignment. The wholly pattern was initially described in 1953 by Gammel as "knotty cypress wood grain".3 The rash spreads over the skin at a rate of about 1 cm a day, and may leave a similarly patterned scale in its wake. It is not raised, and is associated with pruritus (50%) and cosinophilia.

Q2: What underlying diseases does it suggest?
The rash is most commonly associated with internal malignancy. In one literature review of 49 cases the most common accompanying neoplasms were bronchial (32%), or were found in the oesophagus (8%) or breast (6%), or were unidentified metastatic malignances (6%); less common were tumours of the pharynx, stomach, bowel and pancreas, as well as of the genitourinary tract.3 Lymphoreticular neoplasms were under-represented. In addition, the rash has been found in association with tuberculosis, limited systemic sclerosis (CREST syndrome), secondary Sjogren's syndrome,3 virginal breast hypertrophy 1 and hyperesinophilic syndrome, although most of these are single case reports. In about 20% of cases, in whom follow up has continued for one to three years, there is no associated underlying disease.4

Final diagnosis

Merkel cell carcinoma.

Discussion

Erythema gyratum repens is one of several paraneoplastic eruptions which, while rare, are important for signifying the presence of internal malignancy. Such rashes often precede the clinical identification of an underlying tumour by months or years. Consequently, their discovery should prompt an extensive screen for occult malignancy which needs to be repeated regularly for at least several years, but possibly up to 5–10 years after the rash's disappearance. Examples of some of these rashes are listed in Table 1.5

These rashes have in common the fact that they do not arise from malignant infiltration of the skin, or from local tumour pressure effects (for example, lymphoedema), but are the result of immune, metabolic or endocrine effects, that have been identified in only some cases.

In the case of erythema gyratum repens evidence exists for an immunological basis.5 Techniques employing immunohistochemistry have shown a B cell lymphocytic and eosinophilic infiltrate around dermal vessels, with an inconsistent presence of immunoglobulin and C3 deposits in either the basement membrane or epidermis. Theories for the rash's aetiology include cross reaction of tumour antigens in association with specific human leucocyte antigen (HLA) haplotypes or immune complex deposition.7 Interestingly, the rash conforms in its spatiotemporal pattern to that seen in a chemical reaction diffusion model—the Belousov-Zhabotinskii reaction—that describes other biological patterns, such as that found in slime mould.9

Rashes with a paraneoplastic association may also occur in patients in whom no malignancy is ever found, despite extensive investigation and follow up. Moreover, such rashes have a tendency to co-occur: there are several reports of erythema gyratum repens coexisting with pemphigus, pemphigoid, ichthyosis, hyperkeratotic palms and soles, and pсорiiform lesions.

Erythema gyratum repens appears to persist in those cases where carcinoma is recognised, but it may resolve with steroid treatment in both patients with and without coincident malignancy.5 Dapsone has also been effective in a patient with hyperesinophilic syndrome.3 In the one case associated with Sjogren's syndrome, secondary to rheumatoid arthritis, the rash appeared episodically, corresponding to adjustments (up and down) to the dose of prednisolone.7 Our patient's dose of prednisolone remained constant throughout.

Course

The patient was screened for occult malignancy, but thorough clinical examination, an oesophagogastroduodenoscopy, barium enema, and computed tomography of the

Table 1

<table>
<thead>
<tr>
<th>Rash</th>
<th>Common associated malignancy</th>
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<tbody>
<tr>
<td>Erythema gyratum repens</td>
<td>Bronchial carcinoma</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>Bronchial carcinoma</td>
</tr>
<tr>
<td>Necrotizing migratory erythema</td>
<td>Pancreatic glucagonoma</td>
</tr>
<tr>
<td>Superficial migratory thrombophlebitis</td>
<td>Pancreatic glucagonoma (Trousseau's sign)</td>
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<tr>
<td>Acanthosis nigricans</td>
<td>Gastrointestinal malignancy, especially gastric</td>
</tr>
<tr>
<td>Flushing</td>
<td>Carcinoid</td>
</tr>
<tr>
<td>Nodular papillulits</td>
<td>Pancreatic carcinoma</td>
</tr>
<tr>
<td>Ichthyosis/pruritus</td>
<td>Lymphoma</td>
</tr>
</tbody>
</table>

Other: Hypertrichosis lanuginosa, hyperhidrosis, hyperpigmentation, hyperkeratosis.
thorax, abdomen, and pelvis failed to identify any neoplasm. A skin biopsy showed non-specific acute inflammatory changes, consistent with a toxic erythema. The rash was seen to disappear and then reappear over a two week period. It was not seen again over the remaining 13 months of her life. Her cause of death was staphylococcal septicemia that she acquired after a leg amputation, performed for osteomyelitis of the right foot.

In the majority of cases of erythema gyratum repens associated with malignancy, the tumour was diagnosed within seven months of the rash appearing; the longest time was six years.1

Final diagnosis
Erythema gyratum repens associated with secondary Sjögren’s syndrome.

References
1 Gammel JA. Erythema gyratum repens. AMA Archives of Dermatology and Syphilis 1953; 69: 600.

A 15 year old girl with fever, jaundice, haemolysis, and sudden clinical deterioration

Q1: What does the liver biopsy show (see p 250)?
A portal triad with marked oedema and fibrosis extending towards other portal triads is shown in fig 1A. Focal mononuclear cell infiltrates, ductular proliferation, and interface hepatitis are also visible. In fig 1B, hepatocyte ballooning and lytic necrosis are associated with feathery degeneration.

These morphological findings are insufficient by themselves to establish a diagnosis since they are shared by a number of different liver diseases.

Q2: What is the most likely diagnosis?
The differential diagnosis in this case must include all the most important causes of fulminant hepatic failure both acute and chronic. Nevertheless, fulminant Wilson’s disease should be considered the leading diagnosis. The three most relevant clues pointing to Wilson’s disease are the age of the patient, the presence of Coombs negative haemolytic anaemia, and the low serum alkaline phosphatase level. Liver biopsy findings are compatible with Wilson’s disease, since the vast majority of Wilson’s disease patients have evidence of fibrosis, despite widely varying levels and patterns of hepatic inflammation and injury.

In other causes of fulminant hepatic failure, anaemia is not uncommon, and it is usually due to either bone marrow aplasia or coagulopathy and bleeding. Amanita phalloides releases a potent haemolysin, which, however, is not absorbed by the gastrointestinal tract and is not involved in the pathogenesis of signs and symptoms of the intoxication. An association between fulminant Wilson’s disease and haemolysis is reported only in patients where obstruction of the hepatic veins complicates paroxysmal nocturnal haemoglobinuria (a chronic disease). Haemolysis is one of the cardinal manifestations of HELLP syndrome, which, however, is a late complication of pregnancy: being due to red cell membrane injury, in patients with HELLP syndrome a peripheral blood smear must show red blood cell fragments and/or split blood cells with a thorny or spiculated surface.

A further possibility to be considered is leptospirosis, where haemolysis can contribute to anaemia, since exposure to environmental sources, in the present case, was possible or even likely. In Well’s syndrome, however, haemolytic anaemia is invariably of the microangiopathic type.

Course
The attending physicians considered fulminant Wilson’s disease and leptospirosis, mainly in view of the history to exposure to rat excrement, the two most likely diagnoses. Direct and indirect methods of leptospirosis detection, including a search for leptospira DNA in the blood by the polymerase chain reaction, were negative. The hepatic copper content was 600 µg/g dry weight (normal <50). The patient was listed for emergency liver transplantation, but she died of multigraft failure 36 hours later before a suitable organ could be found. Permission to perform a postmortem examination was denied.

The results of genetic testing, performed on a blood sample sent to a reference laboratory, were obtained only several weeks later, and showed a compound heterozygote genotype (His1069Gln; Val1262Phe).

Box 1: Main causes of fulminant hepatic failure

<table>
<thead>
<tr>
<th>Drugs and toxins</th>
<th>Infections</th>
<th>Vascular diseases</th>
<th>Metabolic diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halothane.</td>
<td>Non-A to E hepatitis.</td>
<td></td>
<td>HELLP syndrome.</td>
</tr>
<tr>
<td>Isoniazid.</td>
<td></td>
<td></td>
<td>Reye’s syndrome.</td>
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<tr>
<td>Valproate.</td>
<td></td>
<td></td>
<td>Wilson’s disease.</td>
</tr>
<tr>
<td>Amanita phalloides.</td>
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</table>

Discussion
Wilson’s disease is a rare inborn error of metabolism (frequency between one in 30 000 and one in 100 000 live births), due to mutations in the recently discovered ATP7B gene. The Wilson’s disease gene encodes for a type 1 P-type ATPase responsible for the transport of copper across cellular membranes, using ATP as an energy source.1 Dietary copper is absorbed in excess with respect to body requirements; since it is toxic, copper excretion is limited by both false positive and false negative results. Kayser-Fleischer rings, golden brown deposits of copper are byproducts of copper excretion, is limited by both false positive and false negative results. Kayser-Fleischer rings, golden brown deposits of copper are byproducts of copper excretion, is limited by both false positive and false negative results.
examination, are absent at the time of presentation in the majority of fulminant cases. Liver histology may show micronodular cirrhosis, without specific features; immunohistochemical techniques for copper staining are notoriously of little diagnostic value. Indeed, in fulminant forms, even measurement of the hepatic copper content, that many would consider the golden standard for diagnosis of Wilson’s disease, may be below the diagnostic level, because of massive release of copper from necrotic hepatocytes. Due to the heterogeneity of the genetic defect, the time needed to perform genetic testing is usually too long to meet clinical needs, although it may be a feasible option in selected patients (for example, in subjects from Sardinia, where 85% of cases are due to only five mutations). For unclear reasons, serum alkaline phosphatase may be low (and sometimes unmeasurable) in fulminant Wilson’s disease: a ratio of alkaline phosphatase to total serum bilirubin of less than 2, in association with an aspartate aminotransferase to alanine aminotransferase ratio of greater than 4 has been considered suggestive of Wilsonian liver failure by some, but not by others. As soon as a diagnosis of fulminant Wilson’s disease is contemplated, the patient should be promptly transferred to a hospital with an active liver transplantation programme. While awaiting for an organ, plasma exchange with fresh frozen plasma replacement should be instituted. This has been shown to be a more efficient method to remove copper from the circulation than haemodialysis, peritoneal dialysis, and haemofiltration, with net copper removal reaching up to 12 mg per session. Final diagnosis Fulminant Wilson’s disease. References


An interesting case of thirst and polyuria

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