An undifferentiated itch in a girl aged 14 years

Will Swansson, Yon Kok, Charlie Yue Wang, Chin-Guan Tan, Susan J Robertson

CASE

A previously healthy female aged 14 years presented with an intractable pruritic eruption of the lower limbs associated with bullae and severe excoriations (Figure 1). The symptoms began abruptly 3 months prior with itchy red scaly papules and plaques on the dorsum of feet and shins bilaterally. This was initially successfully treated with the daily use of methylprednisolone aceponate 0.1% ointment, but symptoms then became progressive and recalcitrant. There was no identifiable trigger. A previous skin biopsy performed in the community showed mild spongiosis consistent with an eczematous process, although there was no previous or family history of atopy. She was subsequently managed with a range of different therapies including potent topical steroids (betamethasone dipropionate 0.05% and clobetasol propionate 0.05% ointments), narrow-band ultraviolet B phototherapy, short courses of oral prednisolone, flucloxacillin 500 mg four times per day for secondary bacterial infection, and cetirizine 5 mg twice daily. Due to her recalcitrant symptoms, she also received empirical anti-scabietic therapy with topical permethrin 5% cream; however, despite all the above treatments, the itch remained refractory, and she was subsequently referred to our tertiary centre for a second opinion.

QUESTION 1

What investigations can a clinician perform to work up chronic pruritus?

ANSWER 1

Chronic pruritus is defined as an itch lasting longer than 6 weeks,[1] and if undifferentiated, should be worked up for an underlying cause.[2] Causes of chronic pruritus include dermatological conditions, systemic conditions, malignancies, neurological disorders, and psychiatric illness, with examples listed in Table 1.[3] If the diagnosis is unclear after history and examination, or the symptoms persist despite initial treatment, clinicians can perform a 'pruritus screen' blood test to identify any underlying disease of the internal organs that may be causing the itch.[4] For this patient, the following screen was ordered (Table 2). However, in this instance, it did not identify a cause for her pruritus. Radiological tests such as a chest X-ray or computed tomography (CT) scan of the chest, abdomen, and pelvis may be beneficial if no cause is identified on the initial screen, particularly if malignancy is suspected.[3] For patients with a visible rash accompanying the pruritus, a skin biopsy should also be considered.

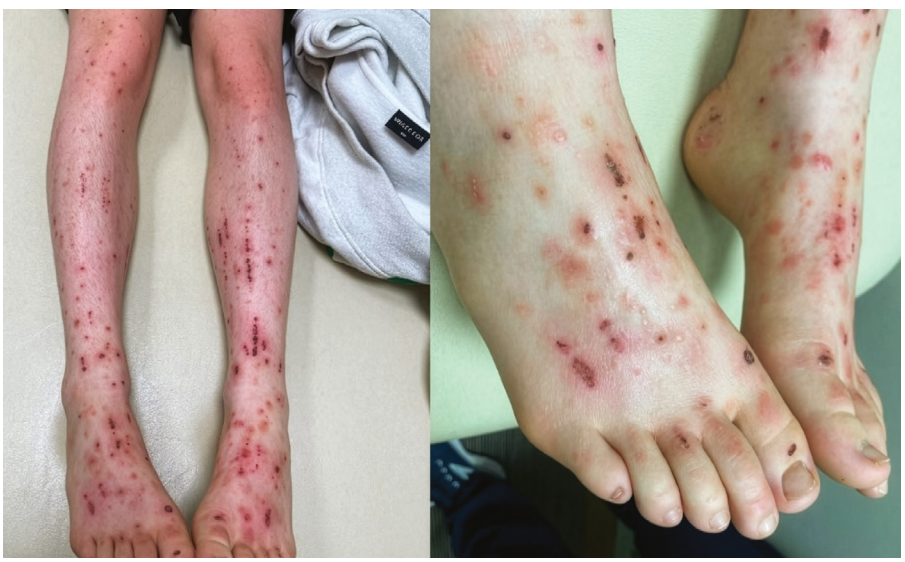

Figure 1. Bilateral lower limb pruritic eruption with bullae and excoriations.

Table 1. Common causes of chronic pruritus

Category	Examples
Dermatological	Atopic dermatitis (eczema)
	Contact dermatitis
	Lichen planus
	Psoriasis
	Scabies
	Urticaria
	Xerosis (dry skin)
Systemic conditions	Cholestatic liver disease (eg primary biliary cholangitis, cirrhosis)
	Chronic kidney disease (uraemic pruritus)
	Diabetes mellitus (diabetic neuropathy)
	Endocrine disorders (eg hyperthyroidism, hypothyroidism)
	Iron deficiency anaemia
Malignancy-associated	Haematological malignancies (eg Hodgkin lymphoma, non-Hodgkin lymphoma, multiple myeloma)
	Solid organ tumours (eg pancreatic, lung, gastric, prostate, breast cancer)
Neurological	Brain tumours
	Multiple sclerosis
	Nerve compression syndromes
	Peripheral neuropathies (eg post-herpetic neuralgia)
	Stroke-related central itch
	Spinal cord lesions
Other	Drug-induced pruritus
	Psychiatric conditions (eg delusional parasitosis, depression, obsessive-compulsive disorder, somatoform disorders)

CASE CONTINUED

One week after the initial dermatology review, the patient presented to the emergency department with acute chest pain and progressive shortness of breath on exertion. She was noted on further history and examination to have anorexia, weight loss, and palpable cervical lymph nodes. A CT scan revealed a mediastinal mass and left-sided pleural effusion (Figure 2). The mediastinal mass underwent ultrasound-guided core biopsy, revealing histological and immunohistochemical features consistent with classical Hodgkin lymphoma, likely of a nodular sclerosing subtype.

QUESTION 2

What is the cause of the patient's dermatological symptoms in this instance?

ANSWER 2

The patient's symptoms are due to paraneoplastic itch associated with Hodgkin lymphoma. Paraneoplastic itch is defined as the sensation of itch as a systemic reaction to malignancy.[2] In Hodgkin lymphoma, the incidence of paraneoplastic itch has been reported to range from 19% in more recent research[5] to 30% in older studies.[6] The phenomenon can also be observed in other haematological malignancies such as non-Hodgkin lymphoma, leukaemia, multiple myeloma, and, to a lesser extent, solid organ tumours.[7] The pathophysiology is not entirely understood, but is thought to involve alterations in T helper 2 cell cytokine expression, notably interleukin 31.[7] In addition to paraneoplastic pruritus, malignancy itself can also cause itch, often due to local tumour-related cytokines or other tumour-specific mechanisms.[8]

QUESTION 3

What are the skin findings in paraneoplastic itch?

ANSWER 3

Paraneoplastic itch may present as normal-appearing skin or feature secondary lesions such as excoriation, prurigo nodules, lichenification, and pigment changes.[2] The symptoms and skin findings can precede other clinical manifestations of the underlying malignancy by weeks or months.[7]

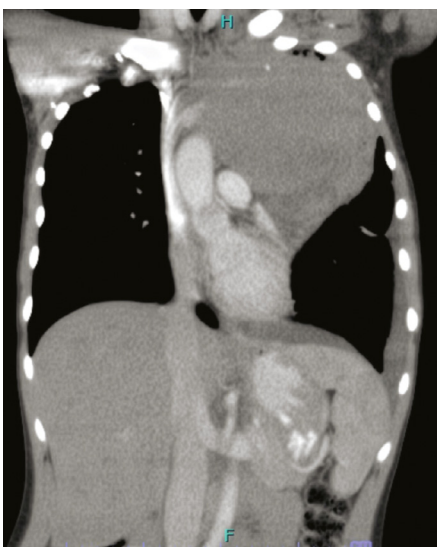

Figure 2. Coronal view of chest CT scan showing a mediastinal mass and left-sided pleural effusion.

CT, computed tomography.

Table 2. Results of pruritus screen performed during initial assessment

Test name	Result	Reference ranges
Full blood examination	Haemoglobin: 116 g/L	120–160 g/L
	White cell count 18.20 x 10^9/L	4.5–13.5 x 10^9/L
	Neutrophils: 14.56 x 10^9/L	1.8–8.0 x 10^9/L
	Lymphocytes: 1.64 x 10^9/L	1.2–5.2 x 10^9/L
	Monocytes: 1.82 x 10^9/L	0.1–1.0 x 10^9/L
	Eosinophils: 0.18 x 10^9/L	0.0–0.5 x 10^9/L
	Platelets: 254 x 10^9/L	150–400 x 10^9/L
Urine, electrolytes, creatinine	eGFR: >90 mL/min	>90 mL/min
	Creatinine: 49 µmol/L	30–80 µmol/L
	Urea: 5.2 mmol/L	2.1–6.5 mmol/L
Liver function tests	Total bilirubin: 1 µmol/L	0–15 µmol/L
	Alanine aminotransferase: 17 U/L	<35 U/L
	Alkaline phosphatase: 133 U/L	100–350 U/L
	Gamma glutamyl transferase: 20 U/L	0–40 U/L
Thyroid stimulating hormone	4.11 mIU/L	0.50–4.50 mIU/L
C-reactive protein	38 mg/L	<5 mg/L
Erythrocyte sedimentation rate	52 mm/hr	2–10 mm/hr
Ferritin	180 µg/L	8–100 µg/L
Vitamin D	56 nmol/L	50–160 nmol/L
Immunoglobulin E Total	1428 kU/L	0–200 kU/L
Strongyloides serology	Negative	–
Coeliac serology	Negative	–
Anti-skin antibodies	Intracellular (ICS) antibodies: 1:10	<1:10
	Basement membrane skin antibody: Negative	–
Enzyme-linked immunosorbent assay (ELISA) dermatology profile	Negative	–
Blood film	Reviewed: monocytosis and neutrophilia suggestive of an acute infection or inflammation	–

eGFR, estimated glomerular filtration rate.

QUESTION 4

What are the histological findings in paraneoplastic itch?

ANSWER 4

The histological findings from an earlier skin biopsy taken in the community showed mild focal spongiosis with lymphocyte exocytosis, as well as mild papillary dermal fibrosis and lymphocytic inflammatory infiltrate confined to the upper dermis (Figure 3). These findings, as is generally the case with paraneoplastic itch,[9] are non-specific and do not necessarily reveal the diagnosis. The histological changes in this instance where thought to represent secondary changes from excoriation of skin due to the symptom of pruritus. While histological examination of skin may not be diagnostic for paraneoplastic itch, it may be useful to exclude other dermatoses.

QUESTION 5

What is the best management of paraneoplastic itch?

ANSWER 5

Paraneoplastic itch can severely affect a patient's quality of life, so effective management is essential. In both adult and paediatric patients, the most important aspect of management is treating the underlying malignancy. A multidisciplinary approach involving oncologists and dermatologists is therefore needed. To date, there have been no large-scale randomised controlled trials examining symptom management of paraneoplastic itch. An expert body has recently published a suggested therapeutic ladder for paediatric patients with lymphoproliferative pruritus.[10] Sedating antihistamines, such as hydroxyzine, are recommended as the first

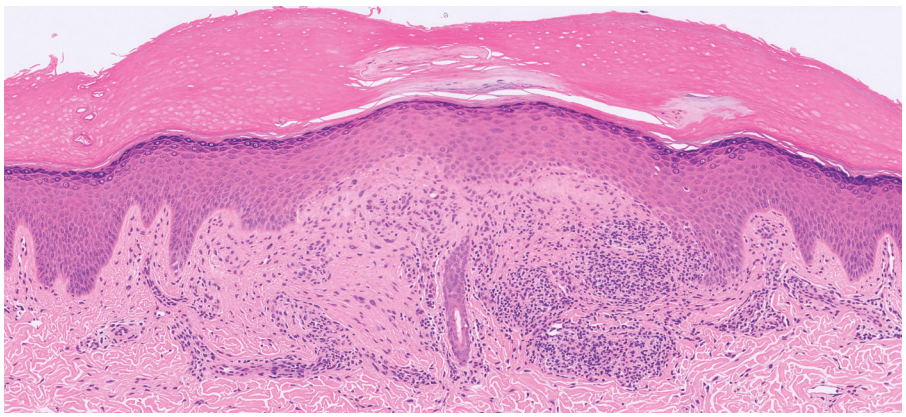

Figure 3. Histological findings from skin biopsy showing mild focal spongiosis with lymphocyte exocytosis as well as mild papillary dermal fibrosis and lymphocytic inflammatory infiltrate confined to the upper dermis (H&E, x 10).

line for nocturnal itch.[10] Other management options include low-dose antidepressants such as mirtazapine, neuropathic drugs such as gabapentin or pregabalin, or oral steroids. There is evidence that narrow-band ultraviolet B phototherapy may also provide benefit.[10] By definition, paraneoplastic itch will typically resolve with remission of the malignancy, but unfortunately, a recurrence can herald a relapse.[2]

CASE CONTINUED

Following diagnosis, the skin lesions were managed with inpatient wet dressings, a soap-free wash, emollients, cetirizine 5 mg twice daily, and topical betamethasone dipropionate 0.05% as required. While there was some symptomatic relief, the most significant improvement of dermatological symptoms occurred with the first cycle of Oncovin, Etoposide Phosphate, Prednisone, Adriamycin (OEPA) chemotherapy.

Key points

- Pruritus can be a symptom of underlying malignancy, particularly haematological cancers, and may even be the initial presenting symptom.
- Clinicians must consider malignancy as a differential diagnosis in paediatric and adult patients presenting with chronic, undifferentiated itch and therefore have a low threshold to reinterrogate the history and examination and perform further investigations.
- Symptoms of paraneoplastic itch generally improve with treatment of the underlying malignancy.

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