Refractory pruritus from malignant cholestasis: management

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Received 3 October 2019
Accepted 23 December 2019

To cite: Fernando GVMC, Preston N. *BMJ Supportive & Palliative Care* Epub ahead of print: [please include Day Month Year]. doi:10.1136/bmjspcare-2019-002051

ABSTRACT

This case report deals with a patient managed in a tertiary-care cancer hospital who suffered pruritus associated with malignant cholestasis. His symptoms were resistant to conventional treatment with ursodeoxycholic acid, chlorpheniramine and cholestyramine. Hence, the multifactorial origin of malignancy-associated pruritus was considered. Correctable factors were corrected and generally the treatment was aimed at possible aetiologies. There were barriers related to insufficient resources available for symptom palliation in this particular setting, which could potentially reduce optimum symptom control. However, various pharmacotherapies and non-pharmacological measures which could potentially have helped relieve pruritus are described and future scope for research in this area discussed.

BACKGROUND

'Pruritus' or 'itch' is a sensory perception which leads to the reflexive act of scratching. It is designated as a 'nociceptive' perception since pruritus likely arises from exogenous (eg, caustic substances) or endogenous (eg, histamine) noxious stimuli which are weaker in intensity than those which generate pain.[1] In cholestasis, interruption of enterohepatic bile acid circulation results in sequestration underneath the skin, an endogenous source of pruritogenic stimulation.

Generally, pruritus is not a common cancer symptom.[2] It is part of the Memorial Symptom Assessment Scale.[3] Pruritus is more commonly associated with specific cancers such as Hodgkin's lymphoma, leukaemia and myeloma.[4 5] In 10% of instances, it is a paraneoplastic manifestation of malignancy.[4] Pruritus may occur from the malignancy itself, resulting in cholestasis, renal failure from treatments like adverse reactions to opioids or targeted anti-cancer therapies.[6 7]

A quarter of those with cholestasis experience distressing pruritus.[8] Common bile duct stenting is considered the gold-standard treatment associated in malignant cholestasis. In conservative management, ursodeoxycholic acid (stimulates hepatobiliary secretions) is recommended.[5 9] Some evidence support the selective serotonin reuptake inhibitor (SSRI) antidepressant sertraline as a safe, effective first-line therapy.[10] Rifampicin can help, but the risk of hepatotoxicity, which could potentially worsen cholestasis, limits its use.[11] The opioid-receptor antagonists butorphanol and naltrexone are not suitable for those on opioids for symptom relief.[12 13] Dronabinol, interferon-alpha, mirtazapine, phenobarbital, propofol, thalidomide and ursodeoxycholic acid are some other options.[1]

CASE PRESENTATION

The patient was a sexagenarian who suffered from progressive dysphagia and significant weight loss for over 2 months before he presented to the hospital. He was diagnosed with advanced adenocarcinoma (stage T4b) in the lower third of the oesophagus, encroaching on the stomach. It was deemed unresectable. The tumour had metastasised to the lower lumbar distant nodes, liver and lumbar vertebrae (including the porta hepatis).

He received chemoradiation to palliate his dysphagia. Two weeks following the completion of radiotherapy, food intake had improved, with a weight gain of 4 kg over the following month. He also suffered from backache, treated with ibuprofen plus omeprazole with satisfactory results.

Two months later, he was re-admitted with worsening anorexia, backache, jaundice, generalised pruritus and weakness. He was referred to the palliative care unit (PCU), where the following management strategies were employed. He had to be discharged after 2 days and managed as an outpatient due to bed shortage.

Case Assessment

Investigations demonstrated cholestatic jaundice (total bilirubin of 80 μmol/L) and elevated serum bile salt levels (32 μmol/L) which were attributed to the porta-hepatis lymphadenopathy. Marginal hypercalcaemia (serum ionised calcium of 2.85 mmol/L) and anaemia (haemoglobin=9 g/dL) were the identifiable causes for the constitutional symptoms like asthenia and anorexia (hypercalcaemia may also cause pruritus).[8]

Renal function was stable making uraemia a remote cause for pruritus. Possible iatrogenic causes for pruritus were ibuprofen and morphine (the latter was introduced at the initial visit).

Case Management

He was started on ursodeoxycholic acid on his initial visit. This is the first-line agent, with multiple mechanisms of action in cholestasis-related pruritus.[8 9] This was combined with the oral antihistamine chlorpheniramine. This was a good choice for two reasons: wide availability in the hospital and as a first-generation (sedating) antihistamine proven superior to second-generation drugs (eg, loratadine) for pruritus.[14] Cholestyramine was added due to inadequate response in the follow-up visit 2 weeks later. Notwithstanding cholestyramine's ability to bind avidly with bile salts thus eliminating them from skin, there is evidence cholestyramine is often ineffective since the blood level of bile salts correlates poorly with clinical pruritus.[15 16]

The single definitive treatment of proven universal efficacy for pruritus from cholestasis is biliary drainage.[8] Despite minimally invasive procedures such as endoscopic ultrasonography or endoscopic retrograde cholangiopancreatography, in our clinical setting with limited resources, patients with cancer do not have access to such sophisticated procedures, and further, the patient stressed his strong aversion towards invasive procedures.

Four pints of blood were transfused and meticulous rehydration done with intravenous 0.9% saline. Intravenous bisphosphonate (etidronate) was administered as a single dose 7.5 mg/kg along with high-dose dexamethasone (24 mg daily in four divided doses), which improved hypercalcaemia, and possibly the related constitutional symptoms and pruritus.[17] Etidronate also potentially contributed towards the relief of back pain associated with vertebral metastasis.[1 17]

Ibuprofen, a non-steroidal anti-inflammatory drug (NSAID), may cause allergy and hence pruritus.[18] However, he tolerated the drug well over the previous 2 months.

Oral morphine at the PCU visit was titrated to analgesic effect, and this had rendered him free of back pain by the second review without worsening pruritus.[19] Since his pain was controlled with oral morphine, it was not prudent to try naltrexone for pruritus since it could exaggerate pain.

Case Outcome

At his second review 2 weeks later in the palliative care clinic, the back pain was still controlled. Fatigue had improved significantly, and his appetite returned. He was unconcerned by the yellowish discolouration of his skin and mucous membranes. The itching continued. He had been discharged from the inpatient facility by the oncology team without notifying the palliative team.

DISCUSSION

The 5-hydroxytryptamine (5-HT_3) receptor antagonist ondansetron, which is of proven efficacy in alleviating pruritus due to cholestasis and sertraline (SSRI), would have been potential options. Parenteral lignocaine is effective for intractable cholestatic pruritus and is a widely available local anaesthetic.[1] Other pharmacological agents are efficacious to varying degrees. Inconveniences in generalised itching has limited the use of bland emollients and levomenthol cream which have also been found to be effective. Non-pharmacological measures like acupuncture, plasma exchange, transcutaneous electrical nerve stimulation (TENS) and ultraviolet-B combined with crotamiton have shown variable promise.[16]

CONCLUSIONS

Malignant cholestasis–associated pruritus can be a troublesome symptom. Therapeutic use of ursodeoxycholic acid combined with antihistamines may fail to relieve the symptom sufficiently. Even though cholestyramine in the standard management of cholestatic pruritus is common in this clinical setting, it is less predictable. Pruritus in malignancy may also be complicated by factors like NSAIDs, opioids or metabolic derangements such as uraemia and hypercalcaemia, which also need to be addressed.

A growing knowledge base on alternative pharmacological and non-pharmacological treatments brings optimism about the future management of pruritus associated with malignant cholestasis. 5-HT_3 receptor antagonists, SSRIs, lignocaine, levomenthol, TENS, acupuncture, plasma exchange and UV+crotamiton are among these novel therapeutic modalities.

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Acknowledgements This article is a modification of one of the assignments submitted by the principal author as part of his Postgraduate Diploma in Palliative Medicine at Cardiff University, UK.

Contributors GF involved himself with the clinical care of the patient, which subsequently led to a discussion with NP. NP guided GF's clinical management in the role of a supervisor. The case report prepared by GF was scrutinised by NP while making additions and modifications. Further, the final overall version submitted for publication is guaranteed for by GF.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

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