

Metastatic Hepatocellular Carcinoma With Paraneoplastic Itch: Effective Treatment With Naltrexone

Brian Keng Yeng Chia MRCP(UK) and Hong Liang Tey MRCP(UK)
National Skin Centre, Singapore

A 62 year-old Chinese gentleman with hepatocellular carcinoma secondary to chronic hepatitis B infection and metastases involving the peritoneum and abdominal wall presented with generalized pruritus of 2 months duration. The pruritus was generalized and particularly severe at night, resulting in insomnia. Physical examination revealed hepatomegaly with a large nodule over the right hypochondrium. There were scattered excoriations over his body but no primary dermatosis or asteatosis was observed.

Laboratory investigations revealed mildly elevated levels of aspartate aminotransferase (43 U/L [15-33U/L]), alkaline phosphatase (122 U/L [32-103U/L]) and gamma-glutamyl transferase (223 U/L [13-63U/L]). Alanine aminotransferase (31U/L [7-36U/L]) and serum bilirubin levels were normal (23 umol/L [5-30]). Parameters of the synthetic function of the liver were also normal, with albumin levels of 39g/L (37-51g/L), prothrombin time (PT) of 10.9s (9.2-11.2s), and activated partial thromboplastin time (aPTT) of 27.5s (27-36.1s). Computed tomography of the abdomen and pelvis revealed multiple heterogeneous masses in both lobes of the liver, with peritoneal nodularity suggestive of peritoneal involvement. The patient was started on emollients, topical corticosteroid therapy, oral anti-histamines, and phototherapy with narrow band ultra-violet B light therapy. However, he did not experience any relief of his symptoms. Due to the intractable nature of his pruritus, the patient was started on oral naltrexone 50 mg per day. He did not experience any side effects and his itch score on a combined visual analogue and numerical scale decreased from 6/10 pre-treatment to 2/10 after three weeks of treatment. The relief in itch was sustained until 10 weeks later when he cut down the dosage to 25mg per day and subsequently stopped taking it altogether due to the high cost of naltrexone. The itch started recurring after he cut down the dosage. With subsequent reinstatement of naltrexone at 50mg per day, his symptoms again abated.

Paraneoplastic itch is defined as itch that occurs early during the natural process or even precedes the clinical evidence of the malignancy, is not caused by the neoplastic mass invasion or compression and subsides after the removal of the tumor. The common prototype of paraneoplastic itch is the pruritus of lymphoma, which can often precede the other clinical signs by weeks and months. Paraneoplastic itch has been anecdotally reported in solid tumors of different types and the severity can range from mild to intractable.

The pathophysiological mechanisms of paraneoplastic itch are poorly understood. In pruritus caused by hepatobiliary tumors, cholestasis from tumor compression of the draining bile ducts is often the cause. However, this was not the case in our patient as the bilirubin levels remained normal. He also had normal parameters of the synthetic function of the liver (albumin, PT, and PTT), indicating that his pruritus was not due to the accumulation of pruritogenic toxins from hepatic dysfunction.

Intense, generalized itch is one of the most common side effects of mu-opioids such as morphine. Though the role of endogenous opioids has not been studied in the setting of paraneoplastic itch, clinical and experimental observations have demonstrated that pruritus can be evoked or intensified by both endogenous and exogenous opioids. This suggests that opioids may have a role to play in both systemic and chronic itch.

The mechanism by which opioids mediate pruritus is thought to be related to their inhibition of the opioid-sensitive interneurons that connect itch and pain neurons. It is generally postulated that the mu-opioid system induces itch whereas the kappa-opioid system suppresses itch. Both Mu-opioid receptor antagonists (MORAs) and kappa-opioid receptor agonists (KORAs) have demonstrated efficacy in chronic and systemic pruritus.

Treatment options for paraneoplastic itch tend to be limited with variable efficacy. Some of the options include selective serotonin reuptake inhibitors (SSRIs) in lymphomas and solid carcinomas, mirtazapine in lymphoma, thalidomide in Hodgkin lymphoma and psoralen plus ultraviolet A (PUVA) in cutaneous T-cell lymphoma. Most of the supporting data for these therapies is based on case series or small-scale studies and focuses mainly on the treatment of paraneoplastic itch secondary to lymphomas rather than solid tumors.

The efficacy of MORAs has been demonstrated in several randomized control trials in the treatment of cholestatic pruritus, chronic urticarial, and atopic dermatitis. In case series and reports, MORAs were also noted to have efficacy in prurigo nodularis, mycosis fungoides, post-burn pruritus, aquagenic pruritus, hydroxyethyl starch-induced pruritus and pruritus of unknown origin. To our knowledge, this is the first reported case of the use of naltrexone in the treatment of paraneoplastic itch from solid tumors.

In this case study, naltrexone was efficacious and safe in the treatment of paraneoplastic itch secondary to metastatic hepatocellular carcinoma. Its efficacy suggests that endogenous opioids may have an important role in the pathogenesis of this condition.

Disclosure

All authors have no relevant conflicts to disclose.

AUTHOR CORRESPONDENCE

Hong Liang Tey MRCP(UK)
E-mail:..... teyhongliang111@yahoo.com