Acute gout during treatment with paclitaxel for metastatic melanoma

Sir, Gout is caused by extracellular urate supersaturation and precipitation in the articular cartilages, tendons or surrounding tissues. Hyperuricaemia is associated with the treatment of fast-growing malignancies, particularly haematological neoplasms. We present a case of acute gout precipitated by the chemotherapeutic agent paclitaxel, used for the treatment of metastatic melanoma, which occurred in the absence of tumour lysis syndrome.

A 61-year-old male with metastatic melanoma and a long-standing mild idiopathic gout presented for a pulmonary metastatic relapse. His gout, of a 20-year course with rare relapses (among which the last one occurred 48 months prior), was treated with long-term allopurinol 200 mg daily. He did not have a history of hypertension, diabetes, renal dysfunction, diuretic use or excessive alcohol intake, and the BMI was normal. The patient was started on paclitaxel at presentation. After the second cycle given at 200 mg/m², marked worsening of his pre-existing chronic periarticular tophaceous deposits occurred, with a 10 times volume increase, accompanied by signs of local inflammation in both elbows, left metatarsophalangeal and all right-fingerPIP areas. This episode was the single-most significant exacerbation of his chronic gout per self report. Prior elevated levels of uric acid in the range of 9–10 mg/dl (540–600 μmol/l) in the past 4 years did not result in clinical exacerbations. No changes in the dose of allopurinol had been made, no new medications were initiated, nor new infections were present and the patient denied any dietary alterations including an increase in his alcohol intake. The uric acid level of 7.5 mg/dl (450 μmol/l) prior to the treatment with paclitaxel remained constant during the treatment with the chemotherapeutic agent, and after its discontinuation. The patient continued paclitaxel for five monthly cycles without improvements in his pulmonary metastases. A progressive increase in the periarticular tophi was noted during treatment with paclitaxel, and local symptoms were controlled with NSAIDs. This case illustrates a marked worsening of gout that occurred in temporal relationship with paclitaxel, satisfying the Naranjo criteria [1] for probable causation. No changes in serum uric acid nor dietary intake of purines were present during treatment with paclitaxel, possibly implicating a direct effect of paclitaxel on tissue crystal homoeostasis rather than an alteration in the pharmacokinetics of allopurinol. Although the latter option, along with chance alone may have led to the development of a gout attack in our patient, we are considering the possibility of an interference of paclitaxel with the uric acid crystal homoeostasis.

Paclitaxel exerts its main therapeutic effect through stabilization of microtubules. This contrasts the microtubule destabilizing effects of colchicine and the chemotherapeutic vinca alkaloids (vincristine, vindesine and vinblastine). The activity of colchicine in gout is mediated through a dose-dependent inhibition of protein tyrosine phosphorylation of proteins that occurs in response to MSU, the organic microcrystals causative of gout. This mechanism relies, at least in part, on the interaction of colchicine with the microtubules [2]. The inhibitory effects of colchicine result therefore in a down-regulation of neutrophil activation by chemotactic factors and inflammatory microcrystals. However, these therapeutic effects have been shown to be reversed in human neutrophils by paclitaxel which, unlike colchicine, has microtubule stabilizing properties [3].

Other opposing effects of paclitaxel to colchicine have been noted with regard to the organizing capacity of centrosomes and kinetochores [4], and to the generation of leucotriene B4 by human PMNs [5], both of which appear to be mediated through interference with microtubule functions.

Convincing evidence links the pathological inflammatory events in gout to changes in the intracellular functions of the microtubules. For example, the release of several chemotactic factors, including the S100A8/A9 protein, from neutrophils represents an important pathogenic mechanism, involving a tubulin-associated pathway, as indicated by its inhibition through...
tubulin depolymerization by vicristine [6]. Another process that plays an important role in gout is the regulation of β-2 integrin-dependent adhesion of neutrophils, which is influenced by paclitaxel [7], through its effects on the adhesion and spreading of downstream immune effectors, such as the leucocytes. Although we believe, based on the stable level of uric acid, that the pharmacokinetics of allopurinol was probably not the major pathogenetic mechanism of the gout attack, it is feasible that unrecognized drug–drug interactions that decreased the bioavailability of allopurinol could have played a minor role. Such an interference can be explained by the fact that hOat2 (human organic anion transporter 2) mediates the transport of both allopurinol and paclitaxel [8]. The normal physiological uricosuric mechanism may also have been impacted by paclitaxel, which has an anti-proliferative effect on renal proximal tubule cells [9] and influences the transport capacity of organic anion transporters such as OAT3, through microtubule disruption [10].

**Rheumatology key message**

- Paclitaxel can precipitate gout by interfering with uric acid metabolism.

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