



Painful swelling of the index finger

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Discussion

The imaging findings in this case are of dense, lobulated, nodular periostitis affecting the hands, ribs, clavicles, and proximal humeri asymmetrically (Figs. 1 and 2). There is no evidence of underlying bone lesion, fracture, or suspicious features. Figure 3 demonstrates the chronic cavitary pulmonary aspergillosis with aspergilloma and the classical Monod Sign.

Despite the imaging findings in combination with clinical features being sufficient for the diagnosis of VIP, the referring hand surgery team made the clinical decision to perform a confirmatory biopsy of the left index finger proximal phalanx. As expected, this demonstrated “non-specific features of new bone formation in keeping with periosteal reaction without sinister features”.

Voriconazole-induced periostitis (VIP) is a recently appreciated disorder with a classical triad of bone pain, raised serum alkaline phosphatase (ALP), and periostitis [1, 2]. Some sources have considered this a form of secondary hypertrophic osteoarthropathy (HOA) [3]. However, they are now considered similar but separate pathologies due to differences in pathophysiological, clinical, biochemical, and radiological characteristics with different management and prognosis [1, 2, 4, 5].

Several pathophysiological mechanisms have been proposed for VIP [5], including a fluoride-dependent

mechanism, similar to that in periostitis deformans seen in fluoride poisoning. Voriconazole is fluoride-based and it has been proposed that its fluoride content causes VIP by stimulating osteoblastic activity and making the extracellular matrix more resistant to resorption [2].

Clinical features of VIP include diffuse bone pain which is almost always present and often severe and resistant to treatment. Symptoms tend to develop within 6 months to 3 years from initiation of treatment [2]. Biochemically, serum ALP and fluoride levels are often raised in VIP [2].

The main imaging findings in VIP are of a multifocal, dense, nodular, and irregular periostitis of benign morphology, which may be symmetrical or asymmetrical and are often demonstrated on radiographs [2, 5]. CT confirms confluent, nodular, or lamellar periostitis with benign morphology [2]. It is not associated with an underlying bone marrow lesion. Enthesopathic changes in the affected long bones can occur [2]. Radiographs/CT are often sufficient to make a radiological diagnosis, but MRI demonstrates irregular periosteal oedema, and bone scintigraphy and FDG PET demonstrate periosteal radiotracer uptake [2]. Almost any bone can be affected bilaterally or unilaterally, including the ribs, clavicles, scapula, acetabulum, and hands [5].

Cessation of voriconazole is associated with rapid improvement of symptoms in weeks to months, resolution of biochemical abnormalities, and improvement or resolution of radiological features. Reduction of voriconazole dose can also be associated with improvement/resolution of abnormalities [2].

This case illustrates many of the classical features of VIP which are discussed above. The imaging findings of multifocal irregular periostitis affecting the hands, ribs, and clavicles are highly suspicious for the diagnosis of VIP, and are not typical for HOA (as discussed below). The clinical and biochemical findings are key to confirming this suspicion. The raised serum ALP fits with the

Diagnosis: Voriconazole-Induced Periostitis (VIP)

The case presentation can be found at doi: <https://doi.org/10.1007/s00256-022-04026-4>.

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Fig. 1 Radiograph of left hand demonstrates dense, lobulated/nodular periostitis (periosteal reaction) of the left index finger proximal phalanx with minimal soft tissue swelling. There is no evidence of underlying bone lesion, fracture, or suspicious features

diagnosis. The patient has a long history of pulmonary TB and subsequent chronic cavitary pulmonary aspergillosis, which in isolation could also be associated with HOA. However, the hand symptoms only started 9 months after the initiation of voriconazole antifungal medication and entirely resolved after cessation of this and switch to alternative antifungal medication.

The main differential diagnosis of VIP is HOA. HOA normally presents with painless finger clubbing, which is part of its classical triad along with periostitis and synovial effusions [5]. This is in contradistinction to VIP which is normally painful, and without finger clubbing [1, 2]. Unlike VIP, serum ALP and fluoride levels are normal in HOA [2]. Periostitis in HOA tends to be smoother, more linear, and more symmetrical than in VIP [2, 5]. VIP often involves areas less frequently involved in HOA, including the ribs and clavicles [1]. Whilst HOA can also be associated with fungal pulmonary infections, it is not associated

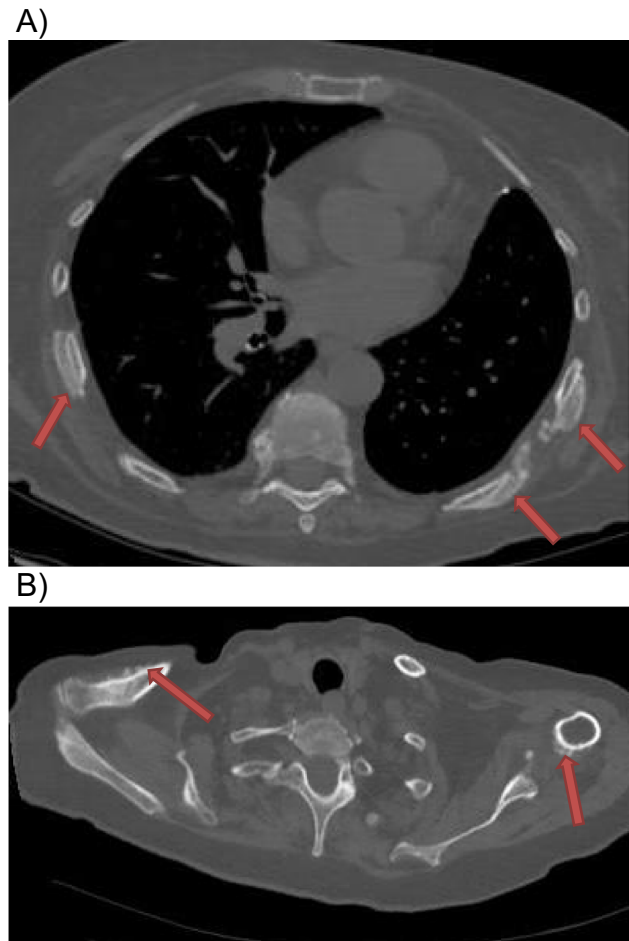


Fig. 2 CT Thorax demonstrates multifocal periostitis (red arrows) of the same morphology as in Fig. 1. It affects the ribs (A), clavicles (B), and proximal humeri (B) in an asymmetrical pattern. Again, there is no evidence of underlying bone lesion, fracture, or suspicious features

with voriconazole and would not resolve due to its discontinuation [3].

When presented with periostitis on X-ray or CT, one must assess its morphology to classify it as non-aggressive or potentially aggressive and to exclude an underlying bone lesion. The morphology and location of the periostitis can also narrow the differential diagnosis. If VIP or HOA is possible, then a chest radiograph would be indicated to assess for a pulmonary cause. Clinical history is key and should be interrogated for possible aetiological mechanisms.

VIP is an under-appreciated disease which is similar to, but separate from, HOA. Differentiating these two pathologies is important due to differences in management and



Fig. 3 CT Thorax demonstrates pulmonary scarring and volume loss in the apical left upper lobe with an air-filled cavity containing a rounded soft tissue density, the classical Monod sign, in keeping with chronic cavitary pulmonary aspergillosis with an aspergilloma

prognosis. An accurate diagnosis of VIP is made based on clinical, biochemical, and radiological findings, and confirmed by response to withdrawal of voriconazole.

Declarations

Conflict of interest The authors declare no competing interests.

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