Joint Bone Spine 86 (2019) 659–660

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Letter to the Editor

Complex regional pain syndrome secondary to everolimus: Two cases

ARTICLE INFO

Keywords:
mTOR kinase inhibitors
Everolimus
Complex regional pain syndrome (CRPS)

In the 1990s, a specific painful polyarticular syndrome [referred as calcineurin inhibitor pain syndrome (CIPS)] was reported in kidney transplant patients who had been on cyclosporine [1,2]. Everolimus has been used as an immunosuppressant in this indication and it is also used in chemotherapeutic regimens for breast and kidney cancer. We report two cases of complex regional pain syndrome (CRPS) attributed to everolimus.

A 52-year-old woman was prescribed everolimus (5 mg/day) for bone and liver metastasis of a mammary adenocarcinoma. Five months after its initiation, she complained of a spontaneous pain with edema in the left foot and ankle extending progressively to the knee and the hip. A physical examination found painful edema in the left ankle without restriction of joint movement. The knee was not hydarthodial, the hip was moderately restricted. The symptoms had regressed spontaneously within three months without everolimus discontinuation. The other case was a 42-year-old man with hypertensive glomerulopathy who was given a transplanted kidney. His maintenance regimen consisted of everolimus (1.5 mg × 2/day) with other immunosupressors. Two months after transplantation, he had pain and edema in his ankles and wrists without trigger. A physical examination showed edema in both hands, wrists and ankles as well as pain in both feet. Everolimus was withdrawn and replaced with mycophenolate mofetil. Two months later, symptoms had completely regressed. In these cases biology and early radiograph were normal. Radiographs recorded few months after the onset of symptoms showed dappled-aspect demineralization. Bone scintigraphy showed uptake in the painful regions in early acquisitions persisting through late bone phases (Fig. 1). MRI of the painful joints showed bone edema (Fig. 2). We diagnosed polyarticular CRPS secondary to everolimus.

Everolimus was only recently introduced into oncology and understanding its possible involvement in the onset of CRPS may be important. CRPS has been reported secondary to the calcineurin inhibitors (tacrolimus, cyclosporine) [3,4]. Data about mTOR kinase inhibitors everolimus and sirolimus (which are used as antineoplastic or selective immunosuppressive agents) as inductor of CRPS are scarce. These two cases are both intrinsic (chronology, no other cause, regression spontaneous or on drug discontinuation) and extrinsic imputability criteria. Previously, four cases of CRPS have been attributed to everolimus [5]. Their clinical presentation were identical to the woman case presentation: unilateral, mono-articular pain in a lower limb with progressive homolateral spread. In our second case, the presentation was different: distal,

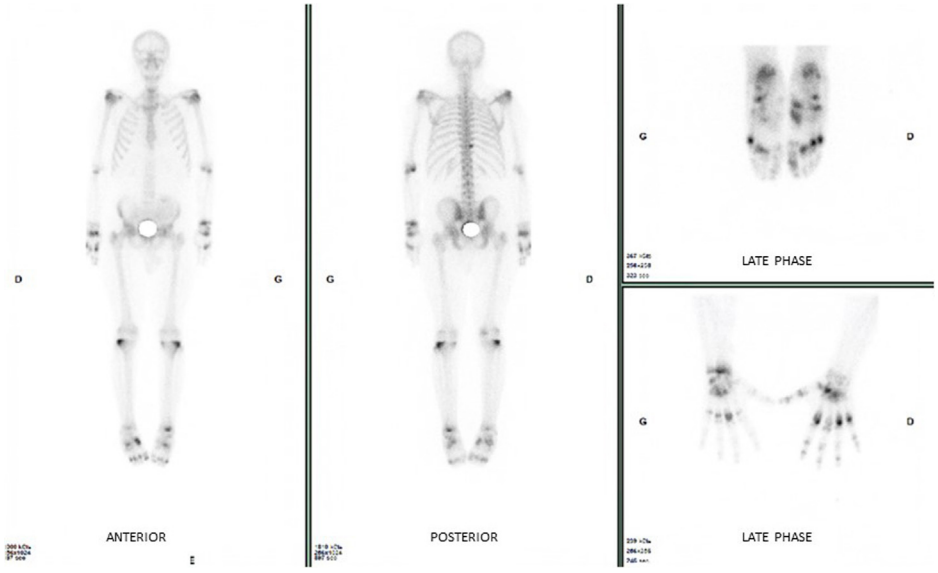

Fig. 1. Bone scintigraphy of a kidney-transplanted man (case 2): multiple subchondral spots of uptake in the hands and feet persisting through late bone phases.

https://doi.org/10.1016/j.jbspin.2019.02.003

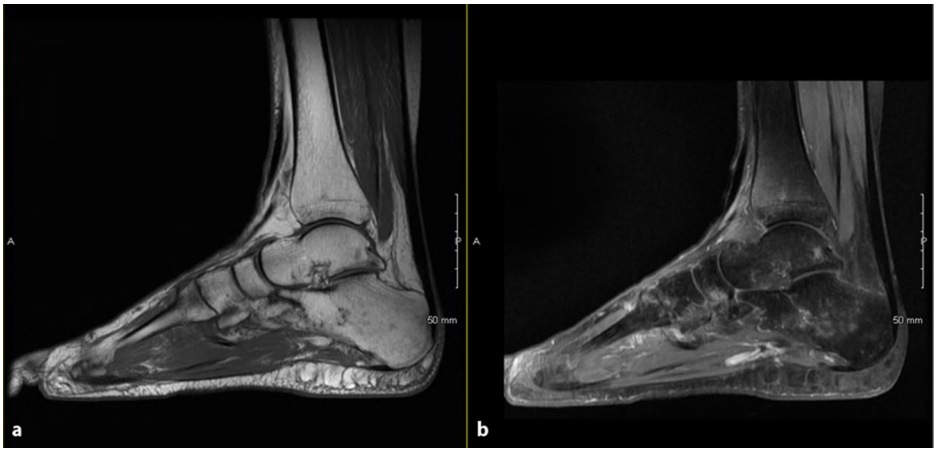

Fig. 2. MRI of the left foot of a women treated with everolimus (case 1): T1 hyposignal (a) increasing after the injection of gadolinium (b) around the spongy bone, the bones in the back of the foot and the tarsus.

polyarticular, symmetrical with major edema. Everolimus belongs to mTOR kinase inhibitors family, as does sirolimus with which cases of CRPS have also been reported [6,7]. The pathogenesis of CRPS remains poorly understood. CRPS could partly be explained by a modification in NMDA receptor activity in spinal cord by anticalcineurin (increasing nociceptive input) [8]. To date, there is no yet rationale to support a toxicity of everolimus on spinal cord or glial cells. Metabolic side effects (hyperglycemia and dyslipidemia) of everolimus could hypothetically be involved [6].

Disclosure of interest

The authors declare that they have no competing interest.

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Available online 15 February 2019