Symmetric metastatic melanoma of unknown primary, presenting as Gorham-Stout syndrome

To the Editor: A 70 years old female patient developed a spontaneous fracture almost 2.5 years ago. Despite the inevitable extensive work-up undertaken in another hospital, no apparent cause for the pathologic fracture was verified and the fracture was treated conservatively but failed to heal. The patient sought medical advice since her condition gradually deteriorated with increasing pain, edema and limb disuse during the last 6 months, prior to her present hospital admission.

The patient, except for the mild pain and the notable edema was in a clinically good condition. Her blood cell count showed no evidence of an infectious process, with normal erythrocyte sedimentation rate (ESR), although an iron deficiency anemia was demonstrated. Blood chemistries showed normal calcium, phosphorus, parathyroid hormone (PTH), liver and renal function indices (creatinine, urea, ALT, AST). An increased C-reactive protein (CRP: 2.2 mg/dL, reference interval: <0.5 mg/dL), an increased lactate dehydrogenase (LDH: 377U/L, reference interval: 90-225 U/L) and a marginally elevated alkaline phosphatase (114U/L, reference interval: 34-104 U/L) were also noted. A conventional X-ray imaging of the right humerous of the patient revealed the virtual absence of the lower section of the diaphysis, suggesting a massive osteolysis of unknown etiology (Fig. 1A). Furthermore, from this finding, a thorough computerized tomography (CT) investigation (thorax, abdomen, head, extremities) revealed another asymptomatic lytic lesion in the contralateral humerous (Fig. 1B). No other bone or parenchymal lesion was observed. A bone scan was also performed with a single-head γ-camera (Siemens Orbiter, Erlangen Germany) after the administration of 555MBq of technetium-99m methylene diphosphonate (^{99m}Tc-MDP). Figure 2 indicates the presence of the lytic lesions seen during the CT scan, while no other lesion was observed.

The orthopedics team proceeded with bilateral arm biopsies, with the presumptive diagnosis of Gorham-Stout syndrome, a rare bone disorder, with 220 cases reported worldwide until 2010 [1-4]. Gorham-Stout syndrome is characterized by uncontrolled and invasive proliferation of vascular or lymphatic capillaries within the bone and the surrounding soft tissues [1-4], accompanied by massive osteolysis. Gorham-Stout syndrome is most commonly seen in pelvis, shoulder girdle or in the long bones of the extremities and it is rarely accompanied by soft tissue or skin lesions [5]. Patient age ranges from one month to 75 years, although children and young adults are most commonly afflicted [6-10]. The etiology of Gorham-Stout syndrome remains obscure, being most likely the result of a complex interplay of growth factors, such as the vascular endothelial growth factor (VEGF), platelet-derived growth factor subtypes (PDGF), angiogenic factors and inflammatory mediators, such as transforming growth factor-β (TGF-β), interleukin-6 (IL-6) and interleukin-1 (IL-1), acting on the characteristic cells of Gorham-Stout syndrome, a cell of the monocyte lineage [11, 12]. Osteoclasts being multinucleated cells partly of mononuclear phagocytic origin, exhibit an increased sensitivity to circulating inflammatory mediators and this appears to cause the observed extensive bone resorption of the Gorham-Stout syndrome [11]. Despite the extensive osteolysis, the osteoblastic activity in Gorham-Stout syndrome is known to remain inappropriately suppressed, as the slightly elevated alkaline phosphatase level shows [1]. The slightly increased serum alkaline phosphatase appeared to support the diagnosis of Gorham-Stout syndrome.

Contrary to the presumptive diagnosis, the histopathologic exaination of the bilateral arm biopsies, performed by Dr Niki Arnogiannaki, verified the presence of malignant

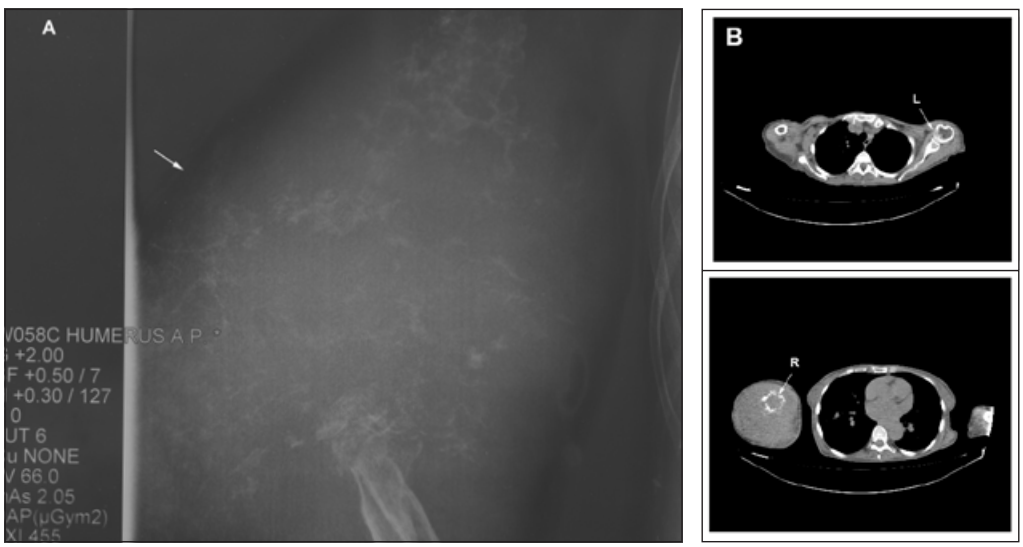

Figure 1. A: X-rays of the right humerous of the patient revealed the virtual absence of the lower half of the diaphysis, suggesting a massive osteolysis of unknown etiology. B: Further investigation of the patient by CT verified the massive osteolysis of the lower section of the right humerous, while another asymptomatic lytic lesion was also seen in the contralateral humerous (the sections correspond to different levels of each arm). The accompanying edema of the left arm is clearly seen, but no other bone or parenchymal lesion was observed.

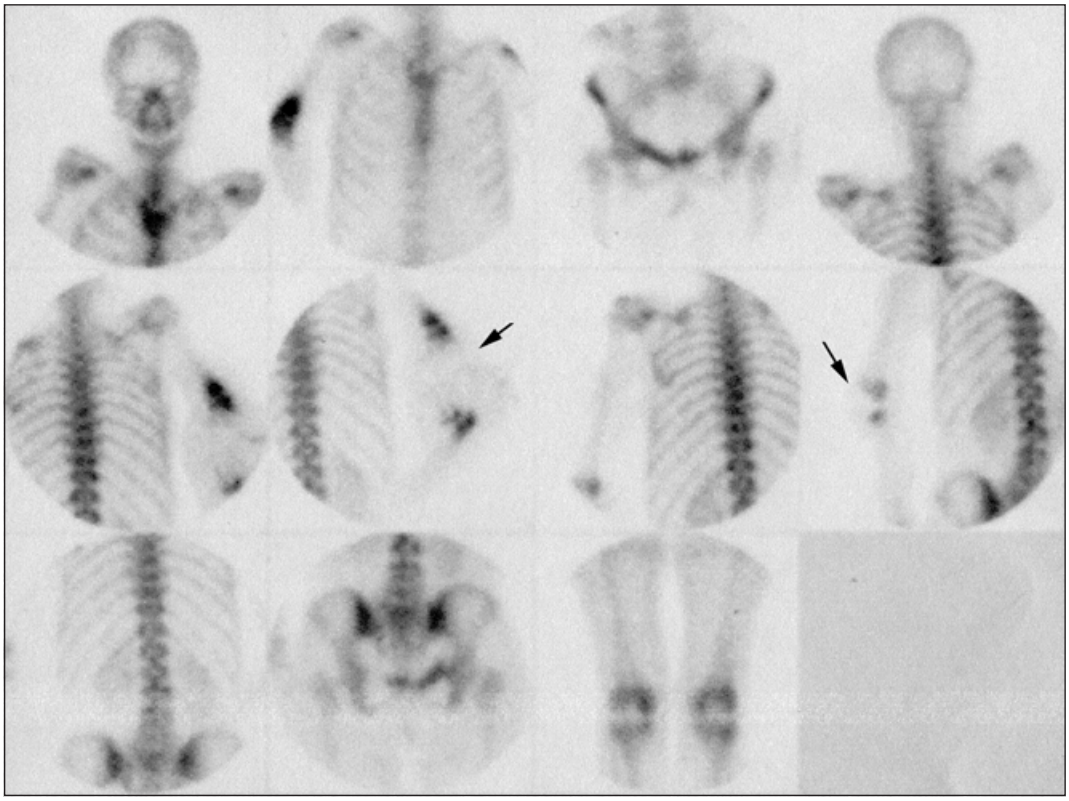

Figure 2. Bone scan obtained 2.5h after the administration of 555MBq of ^{99m}Tc-MDP to the patient. The arrows indicate the presence of the lytic lesions initially seen in the CT scan.

cell mases, with histochemical and immunohistochemical characters of melanoma (positive for melan A and S-100), presumably of metastatic origin, although no primary site was found, despite the extensive work-up. The presentation of a metastatic melanoma of a known primary with exclusive bone involvement [13, 14] occurs in 12% of the cases [13], with spine as the most likely area of involvement. Bone involvement is a late finding in the course of malignant melanoma and the patient usually dies within 4 months. In vitro studies, from tumor associated macrophages (TAMs) isolated from metastatic (lymph node/skin) melanomas and cultured in the presence and absence of osteoclastogenic cytokines and growth factors, have shown that TAMs can differentiate into osteoclasts via either a receptor activator for nuclear factor kB ligand (RANKL)-dependent pathway or via a RANKL-independent pathway, when these cells are co-cultured in the presence of tumour necrosis factor-a (TNF-a) and interleukin 1a (IL-1a) [15]. This observation offers a plausible explanation for the observed massive osteolysis in this case report, further corroborated by the fact that the post-surgical value of CRP, although diminished, it still remained elevated (1.87 mg/dL), since the contralateral arm was still present and infiltrated with malignant melanoma cells secreting factors capable of the observed systemic effects (CRP elevation and osteolysis).

Gorham-Stout or phantom limb or vanishing bone syndrome with malignant melanoma as a cause, with a symmetric pattern and of an unknown primary has never been mentioned in the literature. Therefore, it is suggested that malignant melanoma should be included in the differential diagnosis of Gorham-Stout syndrome. The patient in this case presented serious treatment dilemmas and finally underwent a right humerous amputation. Pending any chemotherapy decisions, the malignant melanoma lesion in the contralateral arm was subjected to radiation treatment, taking into consideration the severe impact of bilateral hand amputation in the quality of life of the patient and knowing the poor outcome of stage IV melanoma patients [14, 16].

The authors declare that they have no conflict of interest

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