Radiotherapy-Resistant Solitary Bone Plasmacytoma of the Clavicle

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Abstract
Solitary bone plasmacytoma of the clavicle is an extremely rare tumor, with an incidence of approximately 0.05% among the primary tumors of the skeleton, defying a challenging diagnostic and therapeutic problem. The absence of particular clinical signs and laboratory tests and the abated sensitivity of modern imagination to differentiate the benign or malignant characteristics of an osteolytic lesion of the distal clavicle impeded a definite diagnosis, which can usually be obtained only after an open biopsy of the lesion. The presented case is distinctive, as it refers to a plasmacytoma of the distal end of the clavicle, which expressed unexplained resistance to both the administrated radiotherapy and chemotherapy. The therapeutic quandary finally resolved after the surgical resection of the entire lesion, leaving the patient free of plasma cell disease 37 months after the initial diagnosis.

Key Words
Solitary bone plasmacytoma · Clavicle

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Introduction

Plasma cell neoplasms account for approximately 1–2% of human malignancies and occur at a rate of about 3.5/100,000 per year [1, 2]. Less than 10% of patients present a solitary plasmacytoma in either bone marrow (solitary bone plasmacytoma, SBP) or a soft tissue site (extramedullary plasmacytomas, EMP). SBP affects fewer than 5% of patients with plasma cell myeloma [3]. The diagnosis is based on histological evidence of a single lesion consisting of monoclonal plasma cells identical to those seen in multiple myeloma, a negative skeletal survey and no evidence of tumor in the bone marrow [4]. Overt into multiple myeloma occurs in almost 50% of patients with solitary plasmacytoma of bone. However, progression may occur as long as 15 years later [5]. We report a case of a solitary plasmacytoma of the clavicle, diagnosed on the basis of persistent symptoms of pain in a young patient with pathological fracture of the distal end of his left clavicle. Failure of local control despite the aggressive radiotherapy and adjusted chemotherapy leads us to surgical intervention and excision of the entire lesion.

Case Studies

A 27-year-old man presented to the outpatient department of our clinic with persistent pain on his left shoulder. He was implicated in a traffic accident 3 months before, and a fracture of the lateral end of his left clavicle had been diagnosed in another hospital. He was treated conservatively with simple hanging of his arm and consequent physiotherapy, but his symptoms were not relieved. Two corticosteroid injections had also been administered without any significant clinical improvement. On physical examination he complained of tenderness in the palpation of his left acromion and lateral end of the clavicle, whereas the motion of his shoulder was quite restricted. Mild effusion of the joint was also present. Plain radiographs revealed an osteolytic lesion of the lateral end of his left clavicle (Figure 1a).

Differential diagnosis included post-traumatic osteolysis of the clavicle and the presence of a neoplastic lesion. The patient had not participated in any kind of sport activities and his occupation (civil servant) was not correlated to repetitive stress to the AC joint. The initial X-rays were not available and, considering the presence of mild discomfort in the AC joint prior to

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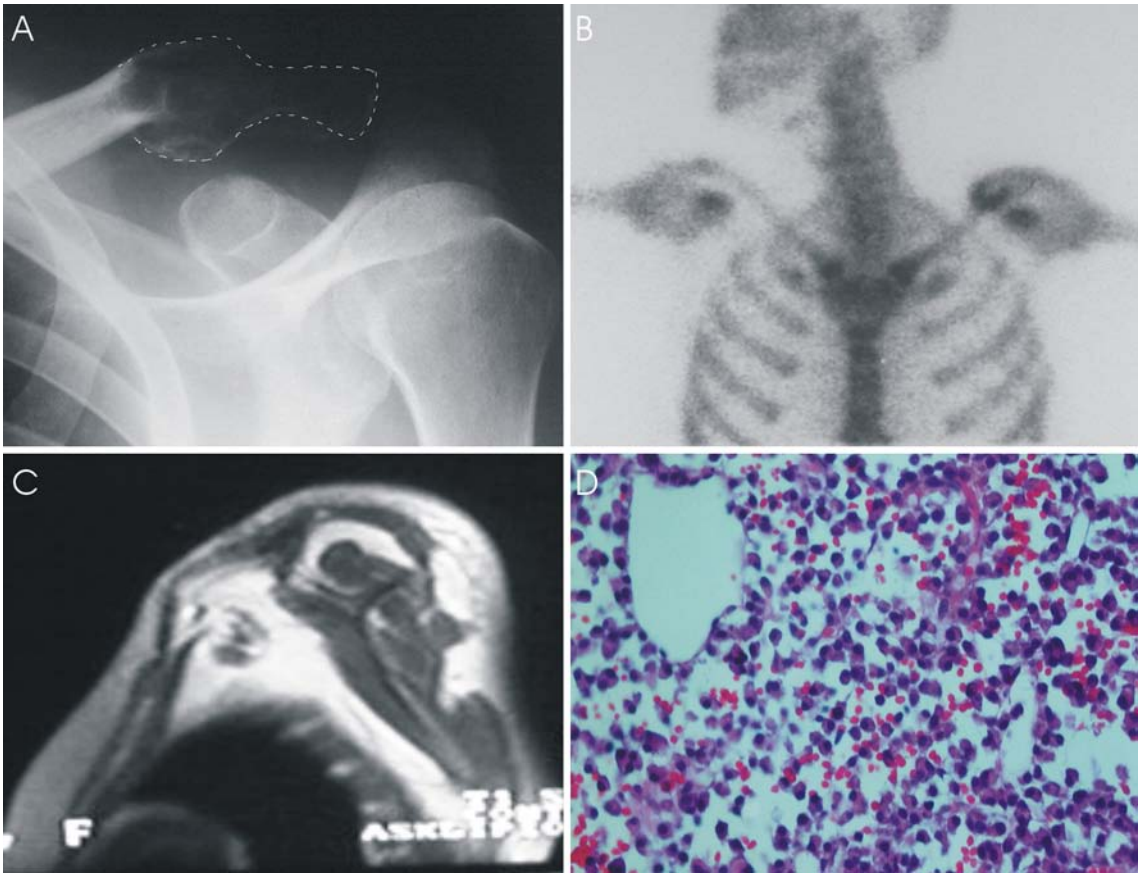
the traumatic event, we presumed that a misdiagnosed pathological fracture might have taken place at that time. The subsequent open biopsy of the involved lesion revealed a solitary plasmacytoma with atypical monoclonal plasma cells positive to λ-chains. A detailed clinical and laboratory investigation was followed in consultation with the Hematological Department of our hospital including: (1) plain radiographs of spine, chest, pelvis, skull and long bones – without any concomitant pathological lesion; (2) a three-phase bone scan (Tc-99mMDP, 16mCi) – showed isolated abnormal uptake at the left clavicle during second and third phases (Figure 1b); and (3) magnetic resonance imaging (MRI) of the left clavicle and computed tomography scan of the thorax – showed disruption of the cortex and sub-periosteal infiltration of the clavicle (Figure 1c) and normal lungs and thoracic wall, respectively. A bone marrow biopsy from the iliac crest showed normal erythropoietic series with no growth abnormalities, whereas complete blood cell count, serum electrophoresis, urinary protein electrophoresis (24-h urine sample), alkaline phosphatase, lactic dehydrogenase, C-reacting protein, ECR and serum Ca^{2+} and PO_4^{3-} were among normal values. The treatment strategy was discussed in the Oncological Council and a decision was made for administration of both regional radiotherapy (45 Gy) and chemotherapy using the VAD (vincristine, doxorubicin, dexamethazone) protocol. After completing radiotherapy and three cycles of VAD, the patient showed no improvement in his symptoms and no change in the radiological and bone scan findings.

Actually, there was a large edema on his left upper quarter of thorax, the supra-clavicular area and the left elbow associated with extreme pain in the region, which limited the free motion of his left arm. Repeated marrow aspiration biopsy and serological markers were negative for systematic disease. A surgical exploration of the lesion, performed 4 months after the initial diagnosis, consisted of resection of the distal midshaft of the clavicular bone along with the surrounding soft tis-



Figures 1a to 1d. a) Plain anteroposterior radiograph of the left clavicle showing an osteolytic lesion of its lateral end, b) bone scan with uptake at the lesion site, c) MRI of the clavicle revealing disruption of the cortex and sub-periosteal infiltration and d) histological examination showing infiltration by atypical plasma cells.

sue envelop. The intraoperative perception of excision of the lesion among normal margins was confirmed by the subsequent biopsy, which could not detect any monoclonal prepotency of the plasmacytoma. The tumor consisted of cumulus of atypical plasma cells (Figure 1d) infiltrating the cortex and part of the periosteum. Isolated atypical plasma cells were also found at the distal part of the specimen whereas the immunostaining studies were negative. The patient did not receive any further treatment and the hematologists regularly followed him for any progression to multiple myeloma. No evidence of local recurrence or overt to systematic disease exists till now, 37 months after the initial presentation.

Discussion

Solitary bone plasmacytoma is uncommon, with an incidence of 5% among patients with plasma cell neoplasms, occurring more commonly in men (65 vs. 35% in women) with a median age of presentation about a decade younger than that of patients with multiple myeloma (55 vs. 65 years) [3–5]. Criteria for identifying SBP differ among varying authors, as some include patients with more than one lesion and elevated levels of myeloma protein and exclude patients whose disease progressed within 2 years or whose abnormal protein persisted after radiotherapy [6, 7]. With the use of sensitive diagnostic techniques such as flow cytometry, polymerase chain reaction (PCR), molecular detection of heavy- and light-chain gene rearrangements and MRI for sampling a larger volume of bone marrow, the current accepted criteria as defined by Dimopoulos et al. [5] are as follows: (a) a single area of bone destruction due to clonal plasma cells, (b) normal marrow without clonal disease, (c) normal results on a skeletal survey and MRI of spine, pelvis, proximal femur and humerus, (d) no anemia, hypercalcemia or renal impairment attributable to myeloma and (e) absent or low serum or urinary level of monoclonal protein and preserved level of uninvolved immunoglobins.

SBP may involve any bone, but it has a predisposition for the red marrow – containing axial skeleton, particularly the thoracic vertebrae. Spinal disease is observed in 34–72% of cases whereas involvement of a rib, sternum, clavicle or scapula has been referred in up to 20% of the cases [5, 8]. The most common symptom at presentation is pain at the site of the skeletal lesion due to bone destruction by the infiltrating plasma cell tumor [9] but patients with vertebra involvement may also have compression fractures of the thoracic and lumbar vertebral or evidence of spinal cord or nerve root compression. Other physical findings, in relation to the site of involvement, might present as a painful mass or a pathologic fracture as in our case. On plain radiographs, SBP classically has a lytic appearance as in our patient, with clear margins and a narrow zone of transition to healthy surrounding bone [5]. Cystic lesions, trabeculated lesions resembling a giant cell tumor or an aneurysmal bone cyst and sclerotic lesions have also been described [10].

Post-traumatic osteolysis of the clavicle must always be taken under consideration as it demonstrates similar clinical, radiological and MRI characteristics to SBP [11, 12]. Usually, there is a history of trauma or repetitive stress to AC joint as in weight lifters but cases of unknown etiology had also been reported, as demonstrated on histological sections of chronic inflammation and reactive changes of the articular surface of the clavicle [13]. Cahill [14] reported on 45 male athletes (44 weight lifters) and noted the presence of microfractures in the subchondral bone in 50% of his series. He proposed that repetitive microtrauma can cause subchondral stress fractures and bone remodeling. Open biopsy is sometimes necessary and various abnormal findings, including extensive hyperemia, periarticular erosions, remodeling of subchondral bone, synovial proliferation and fibrosis, could be observed. The characteristic finding is osteoclastic resorption with signs of osteogenesis [11, 14]. Our decision to investigate the lesion with open biopsy was mainly based on the absence of clinical improvement 3 months after the initial injury despite the prolonged time of immobilization. The extent of the lysis and its radiological characteristics, which were not so typical of a post-traumatic lesion, also contributed to our decision.

Local radiotherapy is the treatment of choice [3, 5, 15, 16]. Treatment fields must include a margin of healthy tissue and for spinal lesions, at least one uninvolved vertebra. Local control could be expected in 88–100% of patients, and virtually all patients have major symptom relief. The local tumor recurrence rate has been reported as being less than 10%. The likelihood of developing subsequent progression of disease depends on the adequacy of the staging procedures and the intensity of radiotherapy. Local failure has also been reported in 15.6% of patients who received less than 45 Gy compared with none amongst those receiving 45 Gy or more [16]. Local recurrence after 45 Gy, as in our case, indeed appears rather exceptional and although failures at equivalent or higher doses have been described these tend to be in particularly bulky lesions [17, 18].

No defined role exists for chemotherapy treatment of SBP. Adjuvant chemotherapy, subsequent to radiotherapy, has been claimed by some to prevent the progression of SPB to myeloma [2], although

others have indicated that chemotherapy merely delays the time to conversion (from 29 to 59 months) but without influencing the overall survival [17]. The toxicity of such treatment precludes its routine use in all patients with SPB.

Furthermore, the absence of widely accepted prognostic indicators for progression also precludes its use on a selective basis in those patients who might be at the greatest risk of subsequent dissemination. The decision to administrate both radiotherapy and chemotherapy in our patient was based on the facts that the treatment was delayed by 3 months and the patient was too young. Despite this aggressive initial treatment the lesion did not respond and the decision for surgical intervention was taken.

In general, surgical resection is not advised for the treatment of SBP although spine instrumentation, prophylactic nailing or other procedures are sometimes necessary to try to re-establish the normal architecture of the spine or other bones affected. Surgical excision was the mainstay treatment option in our case as both radiotherapy and chemotherapy had failed.

Concerning the course of the disease, most cases of SBP progress inexorably to multiple myeloma at a rate of 54–84% at 10 years and 65–100% at 15 years. The median onset of conversion to multiple myeloma is 2–5 years with a 10-year disease-free survival rate of 15–46%. The overall median survival time is 10 years and 20% of patients die of unrelated causes [3, 15]. Finally, prognostic features for conversion of SBP to multiple myeloma, although controversial, include lesions with size > 5 cm, age of 40 years and older, high M protein levels, persistence of M protein after treatment and involvement of the spine [15]. As our patient had none of the above risk factors we believe that it is possible to remain free of any conversion to systemic disease in the future. To date, 37 months after the initial presentation, he is free of symptoms and with excellent functional rehabilitation of his shoulder (Figure 2).

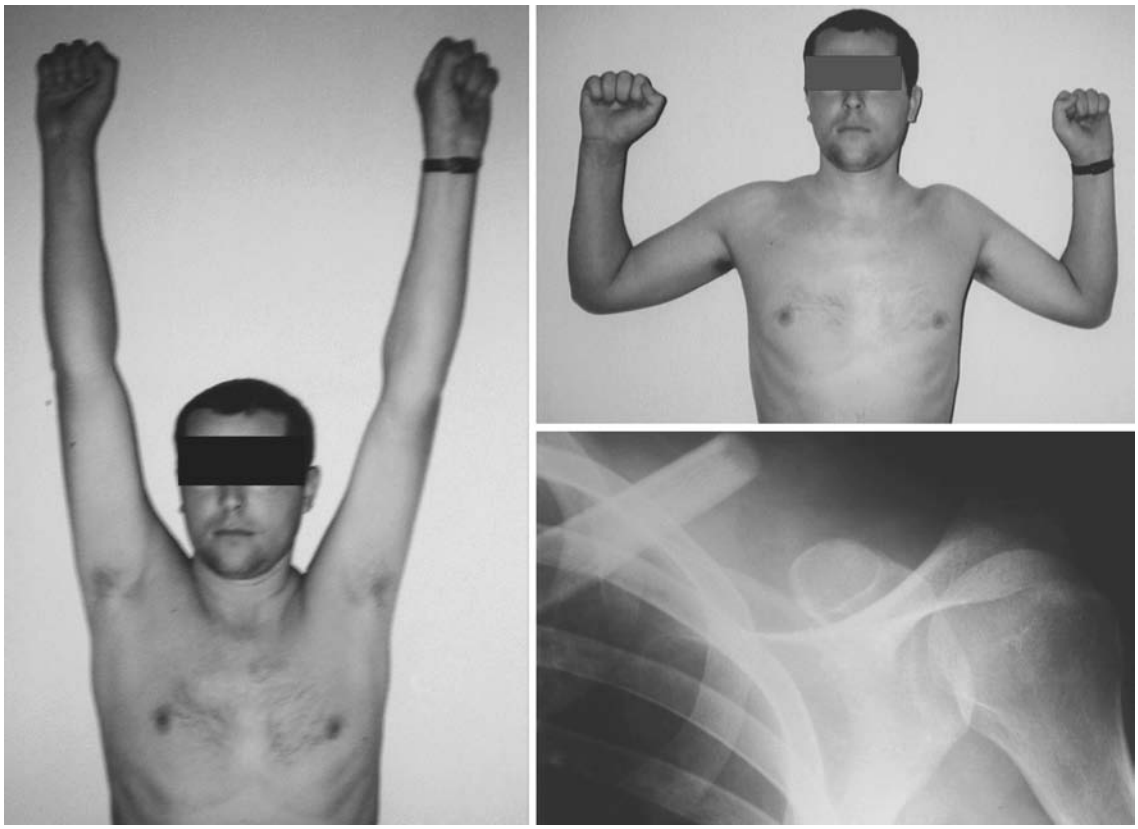


Figure 2. Plain radiograph of the excised lateral midshaft of the clavicle and excellent shoulder function, 37 months postoperatively.

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