

CASE REPORT

A case of severe arthralgia with malignant mesothelioma-associated hypertrophic osteoarthropathy

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Funding Information

No sources of funding were declared for this study.

Received: 3 June 2016; Revised: 28 July 2016; Accepted: 11 September 2016

Clinical Case Reports 2016; 4(11): 1057–1060

doi: 10.1002/ccr3.709

Introduction

Malignant pleural mesothelioma is rare disease, but patients with asbestos-related mesothelioma have increased in numbers over the last few decades [1]. Hypertrophic osteoarthropathy (HOA) is characterized by the coexistence of digital clubbing and periosteal proliferation of the tubular bones. Most cases of HOA associated with pulmonary lesions are lung cancers [2]. Some patients complain of a burning sensation in the fingertips and may also suffer from excruciating bone pain [3, 4]. Herein, we describe a rare case of malignant pleural mesothelioma-associated HOA in a febrile patient who suffered from refractory and painful osteoarthropathy.

Case Report

A 67-year-old man who was a current smoker (0.5 pack/day for 40 years) had a history of asbestos exposure due to his 4-year employment as a miner during his twenties.

Key Clinical Message

Hypertrophic osteoarthropathy (HOA) is a rare syndrome characterized by the abnormal proliferation of dermato-osseous tissue. We report a rare case of malignant mesothelioma-associated HOA who suffered from refractory painful osteoarthropathy. HOA can be associated with malignant mesothelioma and that may be resistant to any treatment.

Keywords

Growth hormone, hypertrophic osteoarthropathy, malignant mesothelioma, vascular endothelial growth factor.

He presented to a local hospital with complaints of productive cough, fever, and right chest pain. On examination, his chest X-ray and computed tomography (CT) scan revealed right pleural effusion, and his serum C-reactive protein (CRP) level was elevated. He was diagnosed as having bacterial pleurisy and was then repeatedly treated with antimicrobial agents, twice as an inpatient and twice in an outpatient clinic. However, the antimicrobial therapy was ineffective and remission and exacerbation of his symptoms and CRP level occurred repeatedly over a 3-month period of therapy. In addition, he presented with dull pain of both wrists 1 month ago. Because of suspicion of having chronic empyema, he was referred to our hospital. Our examination revealed clubbing of the fingers of both hands, particularly the thumbs and forefingers, along with increased pain in the finger, wrist, and shoulder joints. A CT scan revealed right pleural effusion, irregular pleural thickening, mediastinal lymph node swelling, and passive atelectasis (Fig. 1). Analysis of the pleural aspirate could not be performed because of the

strongly coagulated pleural effusion. Histological examination of the specimen taken from thoracoscopic pleural biopsy revealed diffuse proliferating malignant cells with eosinophilic cytoplasm as the epithelial formation. The immunohistochemical analysis showed positive staining for calretinin, cytokeratin 5/6, and epithelial membrane antigen and negative staining for TTF-1, desmin, D2-40, vimentin, CEA, and CD34 (Fig. 2A–D). These results confirmed the diagnosis of epithelioid-type malignant pleural mesothelioma. Extrapleuropulmonary metastatic lesions were absent. Moreover, bone scintigraphy showed the bilateral accumulation of ^{99m}Tc -MDP in the wrist, shoulder, and knee joints (Fig. 3A). An 18F-fluorodeoxyglucose (FDG)-PET/CT scan showed FDG accumulation

in the right pleural lesion, right hilar lymph node, and mediastinal lymph node. Additionally, ring-shaped accumulations were shown in both wrists and the right shoulder joint (Fig. 3B). These findings, that is, clubbing of the fingers, joint pain, and the bone scintigraphy results, were consistent with secondary HOA of malignant mesothelioma. Additionally, his serum level of growth hormone (GH) was elevated at 1.91 ng/mL, as was his serum level of vascular endothelial growth factor (VEGF) at 411 pg/mL. Immunohistochemical analysis showed positive staining for VEGF in the cytoplasm of the tumor cells (Fig. 2E).

The patient underwent chemotherapy with cisplatin and pemetrexed. After one cycle, the serum level of GH

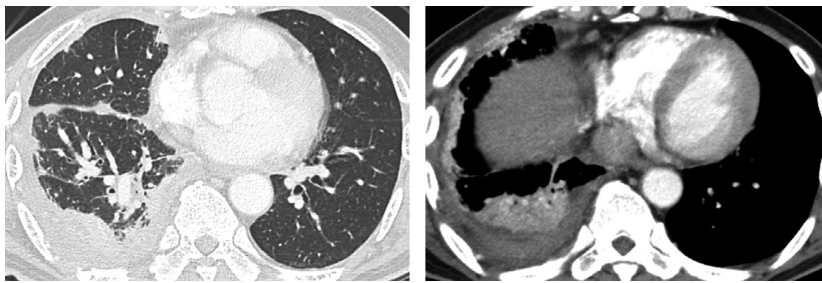


Figure 1. Chest computed tomography images showed right pleural effusion, irregular pleural thickening, mediastinal lymph node swelling, and passive atelectasis.

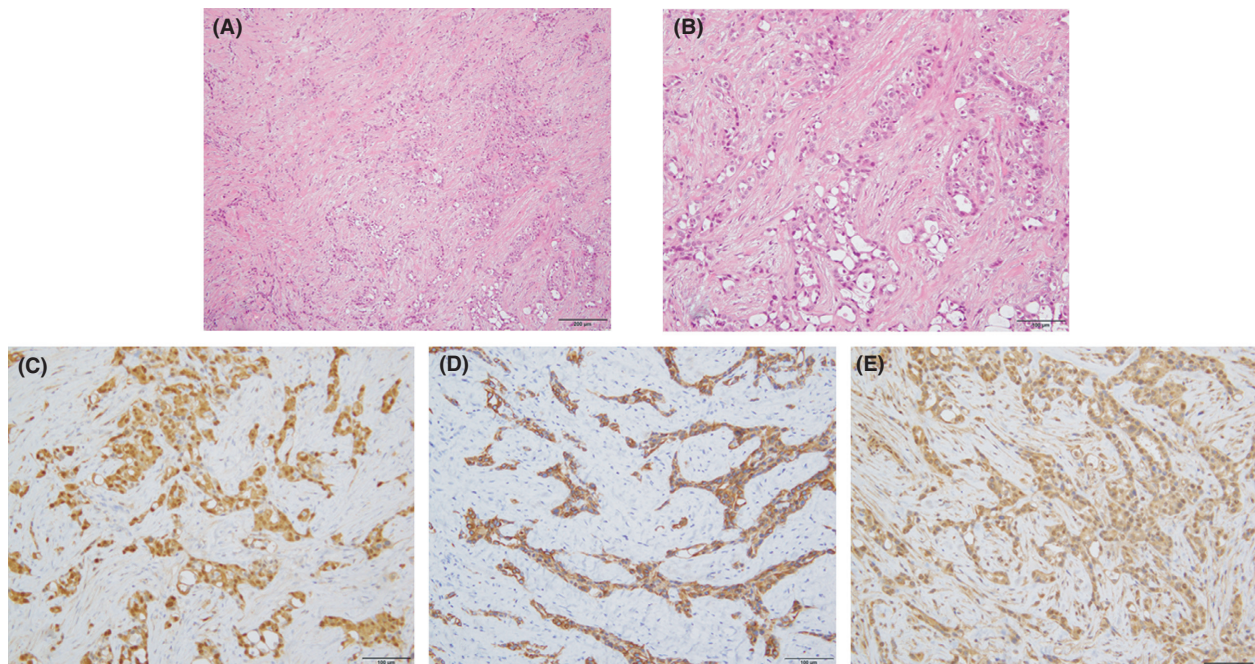


Figure 2. Histological images. (A) The lesion was characterized by the diffuse proliferation of malignant cells (hematoxylin–eosin stain, $\times 100$). (B) These malignant cells appeared with eosinophilic cytoplasm as the epithelial formation (hematoxylin–eosin stain, $\times 400$). (C) Tumor cells stained positive for calretinin ($\times 400$). (D) Tumor cells stained also positive for cytokeratin 5/6 ($\times 400$). (E) The cytoplasm of the tumor cells stained positive for VEGF ($\times 400$).

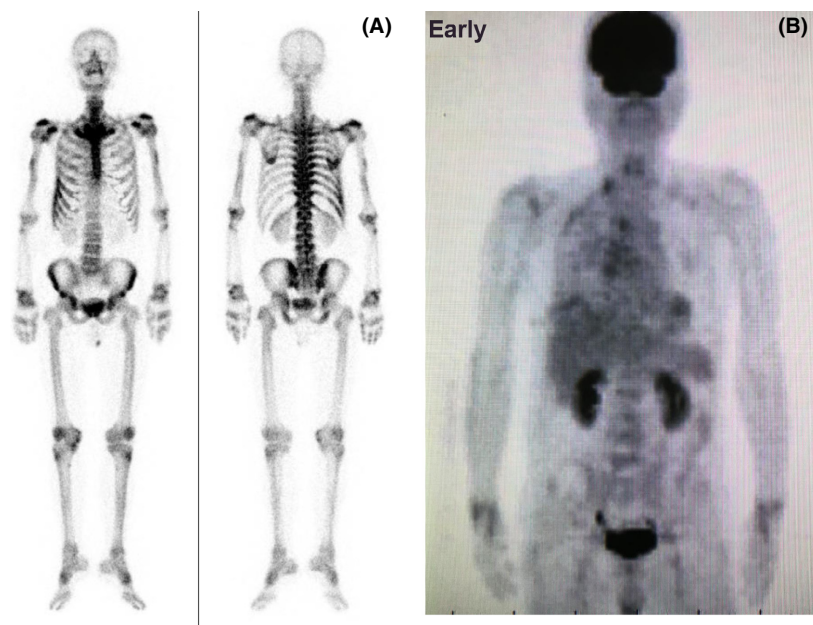


Figure 3. (A) Bone scintigraphy scan showed bilateral accumulation of ^{99m}Tc -MDP in the wrist, shoulder, and knee joints. (B) 18F-fluorodeoxyglucose (FDG)-PET/CT scan showed FDG accumulation in the right pleural lesion, right hilar lymph node, and mediastinal lymph node. Additionally, ring-shaped accumulations were present in both wrists and the right shoulder joint.

fell to 0.6 ng/mL. However, his arthralgia and fever did not improve with the administration of nonsteroidal anti-inflammatory drugs (NSAIDs). Therefore, we initiated oral steroid therapy (betamethasone, 2 mg/day) after the second cycle of chemotherapy. His symptoms slightly improved temporarily, and therefore, the dose of betamethasone was decreased to 1.5 mg/day. Thereafter, however, his arthralgia and fever worsened, and his serum CRP level also rose. After four cycles of chemotherapy, the radiologic response indicated a reduction in the mesothelioma, his disease was considered to be stable, and his serum level of GH had fallen to 0.17 mg/mL. However, his arthralgia and fever continued and worsened when the dose of betamethasone was further decreased. Because our patient was in an extremely weak condition, he was transferred to another hospital to receive palliative treatment as best supportive care, and then died after 9 months at diagnosis as mesothelioma.

Discussion

Hypertrophic osteoarthropathy is a syndrome characterized by abnormal proliferation of the skin and osseous tissues in the distal parts of the extremities. HOA is divided into primary and secondary forms. Primary HOA, also known as pachydermoperiostosis, is a rare heredity condition with variable expressivity. Secondary HOA is most commonly associated with an intrathoracic malignancy, primarily pulmonary malignancies in 80%,

including primary and metastatic lung cancer and intrathoracic lymphoma [2, 5]. The arthralgia of HOA in the present patient developed during the clinical course of mesothelioma. Bone scintigraphy is a highly sensitive method for the detection of HOA. The typical scintigraphic presentation shows diffuse, symmetrically increased uptake in the diaphysis and metaphysis of tubular bones with a distinctive double stripe or parallel track sign [6]. However, although the FDG/PET-CT scan was to a certain degree a meaningful diagnostic tool in our case, the usefulness of this examination is controversial because the pathogenesis of HOA is not mainly metastasis and inflammation but neogenesis of the periosteum [7]. Our patient was diagnosed as having HOA on the basis of the findings of digital clubbing and painful joints and the bone scintigraphy results. In addition, HOA was resistant to conventional treatment with NSAIDs and steroid, although the tumor had shrunk considerably in size with chemotherapy.

This case highlights the following clinical implications. First, HOA can develop in patients with malignant mesothelioma. Wierman *et al.* reported in 1954 that HOA was present in 60% of fibrous tumors of the pleura [8]. In their paper, the detailed correlation between malignant mesothelioma and HOA was not described, and immunostaining, which is considered essential to diagnose malignant mesothelioma, was not performed [9]. The diagnosis of malignant mesothelioma was immunohistochemically confirmed in our patient. Although the precise

rate of occurrence of this condition remains unknown, because the prognosis and survival time of patients with malignant mesothelioma is poor, clinicians might not aware this syndrome for conservative treatment such as opioids, steroid, and NSAIDs. Moreover, there is a highly significant difference between the frequency of digital clubbing in mesothelioma compared with that in benign pleural disease associated with asbestos exposure [10]. Careful examination for malignant mesothelioma-associated HOA should be performed if arthralgia and/or digital clubbing develops in asbestos workers.

Second, mechanisms other than GH and VEGF may contribute to the development of mesothelioma-associated HOA. Generally, the management of HOA is dependent on the underlying disease. Removal of tumors or chemotherapy for cancer can improve or resolve HOA in some cases [5, 11]. Pathogenesis of HOA is not fully understood. One hypothesis involves tumor production and the release of factors such as VEGF and GH into the circulation that promote features of HOA [2, 12, 13]. However, the considerable reduction in tumor size and decreased serum level of GH with chemotherapy did not improve the severe arthralgia in the present patient. As also VEGF, Kao *et al.* reported that the median level of serum VEGF in patients with mesothelioma was 564 pg/mL (range: 79–2580 pg/mL), which was higher than the VEGF level in our patient (411 pg/mL) [14]. Taken together with these reports, the syndrome in the present case was difficult to explain solely by factors such as GH or VEGF. Although the precise mechanism for this is unclear, we surmise that one of the reason that every kind of cytokine could not be regulated for delay in an appropriate diagnosis and therapy.

In conclusion, we describe a rare case of malignant mesothelioma-associated HOA. To the best of our knowledge, severe symptoms associated with HOA in a patient with malignant mesothelioma have not been previously reported. Although HOA is a rare syndrome whose exact mechanism unknown, careful examination for malignant mesothelioma-associated HOA should be undertaken if arthralgia and/or digital clubbing develops in asbestos workers.

Conflict of Interest

The authors state that they have no conflict of interests.

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