

The Adenocarcinoma Lung Metastasis Behind the Pierre-Marie Bamberger Syndrome: A Case Report

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Abstract

Hypertrophic pulmonary osteoarthropathy (HPO) or Pierre-Marie-Bamberger (PMB) syndrome is not very well-known to a large part of the medical community because it's a rare syndrome, which poses a problem when it comes to the differential diagnosis. This uncommon syndrome is characterized by the association of digital hippocratism (DH), polyarthritis and periostitis affecting the long bones. Ninety percent of the cases of HPO are paraneoplastic syndromes, linked to lung cancers, ENT (Ears-Nose-Throat) cancers and rhabdomyosarcomas. In this article, we present the case of a patient with a pulmonary adenocarcinoma who manifested this syndrome concomitantly with a bone metastasis. The diagnostic approach to this case was complex, multi-layered and decisive for the course of the treatment and prognosis of our patient. Furthermore, the published and available literature on both subjects is very scarce which also seems to be related to the fact that such a combination of signs and symptoms is rare. As the pathophysiology of PMB's syndrome is mostly unknown we present some diagnostic hypotheses found in the medical literature. Treatment for this paraneoplastic syndrome is based on treating the cause, which mostly means cancer treatment (chemotherapy, surgery).

Keywords: Pierre-Marie-Bamberger; Osteoarthropathy; Secondary Hypertrophic; Clubbing Fingers; Digital Hippocratism; Adenocarcinoma; Lung Cancer; Lung Neoplasms

Abbreviations

PMB: Pierre-Marie-Bamberger; HPO: Hypertrophic Pulmonary Osteoarthropathy (Same as SHO: Secondary Hypertrophic Osteoarthropathy); DH: Digital Hippocratism

Introduction

Hypertrophic pulmonary osteoarthropathy (HPO) or Pierre-Marie-Bamberger (PMB) syndrome is not very well-known to a large part of the medical community because it's a rare syndrome, which poses a problem when it comes to the differential diagnosis.

We report the case of a patient who presented signs of inappetence, asthenia, as pain at his right ankle during his stay at a rehabilitation center after a surgical procedure for a lung adenocarcinoma stage IV.

This article discusses a case with overlapping metastatic bone lesions and a PMB syndrome.

Case Presentation

A 65-year-old patient, Mr. V., complained to his general practitioner about a scapular pain on his right shoulder that is present since many months. His past and present medical history includes: former smoker of 50 packets-year and a Type II non-insulin-dependent diabetes. The scapular pain reported by the patient is permanent and loud, it's partially relieved by Paracetamol and NSAID.

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A pulmonary radiograph was obtained because of his smoking history (Figure 1). It revealed a pulmonary mass as an opacity in the right upper hemithorax, which generated other complementary investigations. A Positron Emission Tomography Computerized Scan (PET-CT) was ordered and confirmed the presence of a right upper lobar mass in contact with both the large and small pulmonary fissure as well as the posterior pleura, going forward to the pulmonary hilum. A preliminary evaluation also suggested a probable invasion of the upper lobar bronchus. There were also a lower right medial periscapular hypermetabolic muscle mass with bone destruction, suspected of muscle metastasis with bone invasion. Given these findings, an echo-guided biopsy puncture of the scapula was ordered. It confirmed, by histopathologic examination, the presence of an adenocarcinoma of the right upper lobe, stage IV, cT3, cN2, cM1 oligometastatic to the bone level and compatible with a pulmonary origin. A brain MRI excluded metastasis in the brain.



Figure 1: Thoracic X-Ray of Mister V.

During the first two months post-diagnosis, Mr. V. benefited of external radiotherapy (45Gy) at the level of his right scapula and then induction chemotherapy of Navelbine/Cisplatin type every three weeks, both for analgesic purposes.

Three months after the diagnosis, another PET CT assessment control was ordered and showed the persistence of the bulky upper right lobar mass without significant change in metabolism compared to the first PET CT, despite the chemotherapy treatment. A right upper lobectomy was proposed as surgical treatment. The surgical approach compromised the 3rd and 4th posterior ribs as well as a right lymph node.

After the surgical procedure, the patient was admitted to a short-stay rehabilitation center (two month) and then was transferred to our rehabilitation center to undergo his pulmonary rehabilitation and pain management program.

In our rehabilitation center, he presented several signs and symptoms: an inappetence since the beginning of the disease and chemotherapy, a significant asthenia, a nocturia stable at 2x/night, an effort dyspnea that has appeared since the pulmonary resection, a severe constipation (most likely due to the opioid analgesics during the post-op period) and nausea and vomiting during episodes of stress or intense effort, especially during physiotherapy or during transportation. He also complained about pain in his right ankle during mobilization, which has been present for two months. The pain was described as “very disabling” by the patient.

The physical examination of the patient, at this time, revealed a normotensive patient, a tachycardia at 110 bpm, non-febrile, a saturation in ambient air with 98%. The chest auscultation revealed a decreased vesicular murmur compatible with hypoventilation in

the upper right lobe region. We observed hippocratism of the hand fingers. The mobilization of the right shoulder was limited by pain in all directions. In addition, the right ankle was swollen with a painful palpation of the whole area and we noted a decrease in joint motion and muscle strength. However, the biological values exclude inflammatory syndrome, electrolyte disturbances, anemia and organ failure.

We note that the patient’s complaint concerning the pain at his right ankle had persisted for two months. Ankle x-rays were ordered (Figure 2) and showed periosteal appositions evoking a lesion that suggested a PMB syndrome. However, the intense ankle pain that the patient reported is not usually described in PMB syndrome and we think that had nothing to do with the syndrome. For this reason, the patient had a Skeletal Scintigraphy (Figure 3) which revealed a pattern of bone destruction of the posterior part of the right tibial with tissue replacement and significant osteoblastic reaction on all the surrounding bone tissue. This was visible from the early phase of Skeletal Scintigraphy, raising the suspicion of a major inflammatory reaction secondary to the metastatic osteolysis process. A clinical examination was performed to rule out the differential diagnosis of osteitis.



Figure 2: X-Ray of the ankle face (left picture) and profile (right picture): pathognomonic periosteal appositions of PMB syndrome.

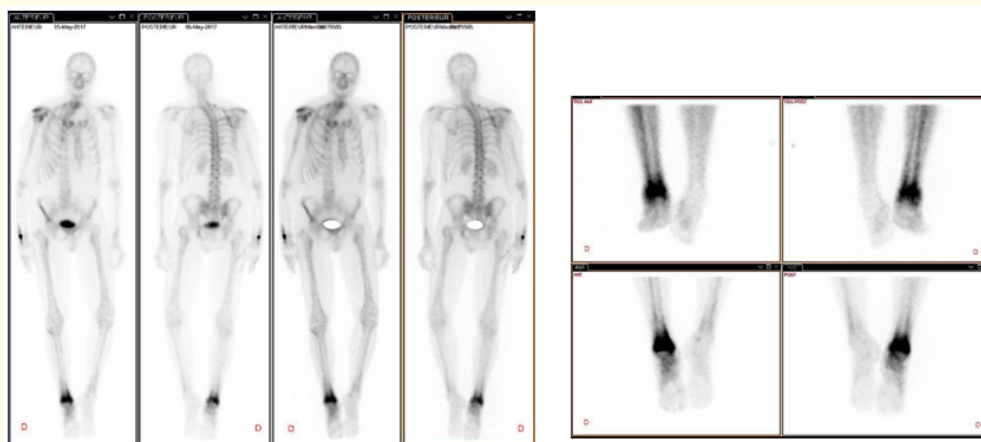


Figure 3: Bone scan (first picture) showing the osteoblastic reaction in the right ankle and (second picture) a zoom on the osteoblastic reaction.

We address Mr. V. f to the main hospital for diagnostic biopsies of the osteoblastic reaction that we see on the Skeletal scintigraphy, but the patient has been sent back to the rehabilitation center without further examinations due to the high probability of PMB syndrome diagnosis because of the ankle x-rays, which showed periosteal appositions as pathognomonic signs. The oncological treatment was continued with analgesic management concerning the ankle pain. However, it was still not possible, at this stage, to exclude a metastatic lesion. This could have changed the therapeutic management, the prognosis and the life quality of Mr. V. Thus, we kept continuing the diagnostic process with a second radiological opinion which recommended a surgical biopsy as the radiological access was too risky. The pathology report of the bone biopsy confirms a bone metastasis whose appearance was superimposed on the known pulmonary adenocarcinoma and which was concomitant with lesions highly suggestive of a PMB syndrome.

Discussion

Pierre-Marie-Bamberger syndrome

The purpose of this article is to discuss about the PMB syndrome. We have illustrated this with the case of Mr. V because the diagnostic approach was rare and interesting. The PMB syndrome, also known as hypertrophic pulmonary osteoarthropathy, remains mysterious and unknown to a large part of the medical community. Because it's a clinico-radiological syndrome, several clinical and radiological criteria must be present to confirm the diagnosis, especially the triad of finger clubbing (DH: digital hippocratism), periostitis and synovitis. DH has been a clinical manifestation known for centuries. The link between DH and pulmonary pathology was first described by Hippocrates in the 5th century BC. He declared "the examination of the thorax begins with the phalanges" [1]. However, no theory has been able to explain completely this phenomenon, whether primary (pachydermoperiostitis linked to autosomal dominant mutation) or secondary etiology (PMB).

The concept of secondary hypertrophic osteoarthropathy (SHO) was developed independently in 1889 by Bamberger [2] and in 1990 by Marie [3]. Ninety percent of the cases of HPO are paraneoplastic syndromes, linked to lung cancers (5 - 10%), ENT (Ears-Nose-Throat) cancers and rhabdomyosarcomas. It is associated more rarely with other intrathoracic diseases (tuberculosis, sarcoidosis, heart diseases...).

DH (or finger clubbing for Anglo-Saxons) is characterized by a deformation of the last phalanges which thicken and widen, thus adopting the appearance of "drum stick" with domed nails and shiny so-called "watch glass". It concerns the hands but also the toes and is the most often symmetrical (Figure 4). (9) (19)

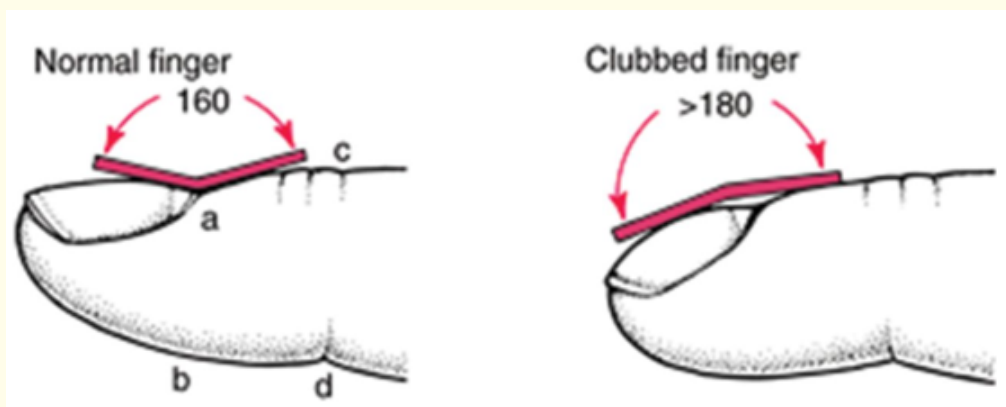


Figure 4: As demonstrated, the normal hyponychial angle is $\approx 160^\circ$, and an angle $>180^\circ$ is consistent with clubbing.
Reprinted from *The Merck Manual of Diagnosis and Therapy* [4].

During examinations with electronic microscope, several modifications were observed in the affected fingers: local hypervascularization with activation of the endothelium, apposition of extracellular tissue and lymphohistiocytotic infiltrate. Arteriography and capillaroscopy reveal hypervascularisation and an increase in the number of distal digital arteries, as well as arteriovenous communications.

The pathophysiology of DH and PBM syndrome seems to be poorly understood, but in the literature, several pathophysiological hypotheses have been mentioned.

In 1961, Ginsburg, *et al.* [5] mentions the implication of an increase in estrogens in the disease. This theory was criticized by multiples opinions thereafter because similar hormonal rates were also described in the case of healthy patients [6].

He will be joined in 1987 by Dickinson, *et al.* [7], who discussed the role of growth factors VEGF, PDGF, megakaryocytes as well as blood platelets in digital clubbing. Currently, this is the most likely assumption (but still controversial). Megakaryocytes must divide in order to give birth to circulating platelets. Most of this fragmentation takes place at hepatic and splenic level. However, a part of the megakaryocytes passes physiologically through the endothelium and go to the blood circulation to the lungs where they will fragment at the level of the pulmonary capillaries. If any pathology leads to divert megakaryocytes from their pulmonary path, they will be able to borrow systemic circulation and go to impact the distal circulation level, mainly in digital capillaries. A massive liberation of various growth factors such Platelet-Derived Growth Factor (PDGF), Vascular-Endothelial Growth Factor (VEGF), and Transforming Growth Factor (TGF) is going to inducing recruitment of monocytes, polymorphonuclear neutrophils and fibroblasts. There is also an effect on the smooth periarteriolar musculature as well as activation of the vascular endothelium. The process results in a matrix extracellular apposition, a modulation of arteriovenous flow and massive angiogenesis at the digital ends, leading to the development of DH (Figure 5).

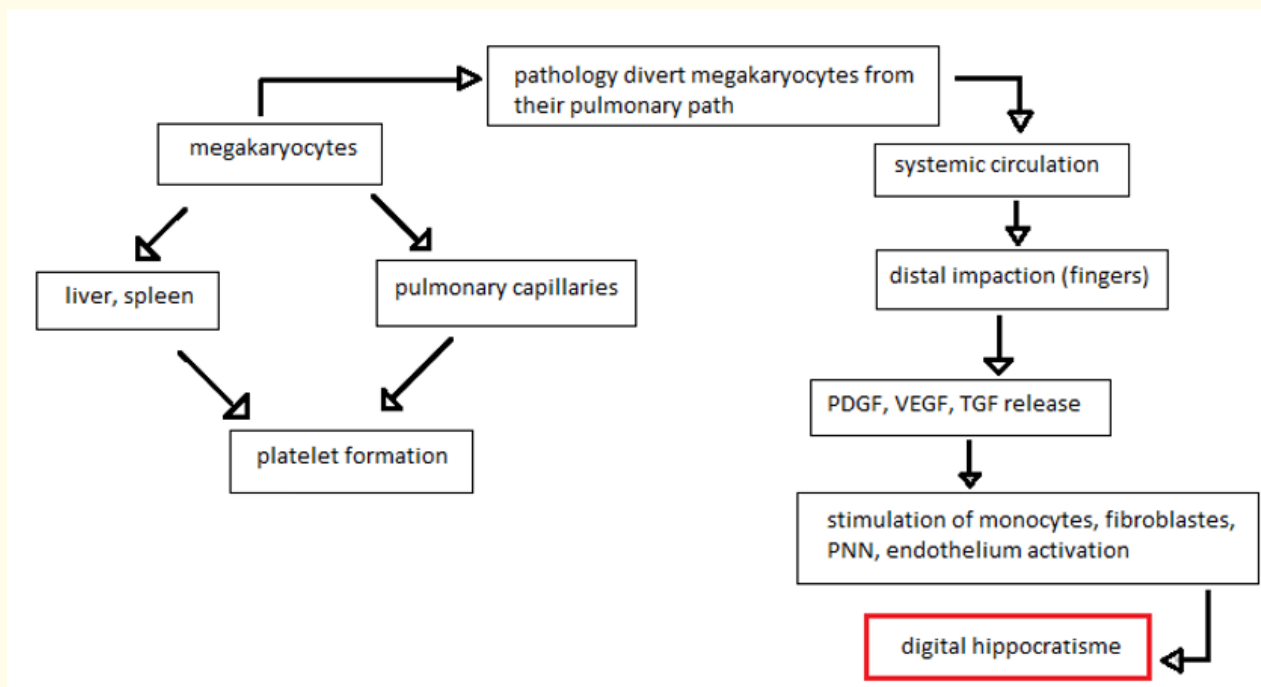


Figure 5: Hypothesis of the link between DH and megakaryocytes. PDGF (Platelet-Derived Growth Factor), (VEGF) Vascular-Endothelial Growth Factor, TGF (Transforming Growth Factor).

Gosney, *et al.* [8], who studied growth hormones in 1990 and their link in digital clubbing, agreed with this explanation.

Traitement of Pierre-Marie-Bamberger disease

The treatment of Pierre-Marie-Bamberger's disease is straightforward in theory but complex to achieve in the clinic. Indeed, the treatment of the causative disorder, in most cases and in our case, is the treatment of the tumor. Recurrences of PMB syndrome have been observed during relapses of the tumor or during the occurrence of metastases. Mr. V therefore has the benefit of oncological treatment and symptomatic treatment with aspirin, NSAIDs, and glucocorticoids.

Regarding the catamnesis of our patient, Mr. V., the metastatic progression of the disease confirmed by the pathology of the bone biopsy performed at the ankle brought back the interest of adjuvant radiotherapy, which no longer found its justification in the treatment. The patient was referred to oncology for palliative treatment. He received analgesic radiation from his right tibia and then returned to his family for end-of-life care [9,10].

Conclusion

The coincidence of secondary hypertrophic osteoarthropathy and bone metastases is unusual and rare, but important to be detected because it changes the patient's therapy and quality of life.

The important point, which we would like to share through this clinical case, is the possible overlapping of different pathologies and that the absence of response to treatment is an important indicator aimed at making us reconsider our diagnosis.

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Disclosure

We declare any conflict of interest. The cited patient gave his entire consent to this article.

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