

Inflammatory Hypertrophic Osteoarthropathy Spectrum with Response to Interleukin-6 Blockade and Subsequent Furunculosis-like Cutaneous Flare: A Case Report

Rashad Jafarov¹, Iqbal Babazade^{2,3}, Riminalida Muradova¹, Nihad Asadov¹

1. Department of Rheumatology, Saf Hospital, Baku, Azerbaijan.
2. Alturamedix Academy of Emergency & Critical Care, Baku, Azerbaijan.
3. Medical Unit, National Defense University, Nakhchivan, Azerbaijan

ORCID: <https://orcid.org/0009-0000-9631-209X>

ORCID: <https://orcid.org/0009-0004-8400-1867>

ORCID: <https://orcid.org/0009-0008-6660-7063>

ORCID: <https://orcid.org/0009-0001-2224-0860>

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Abstract

Pachydermoperiostosis, or primary hypertrophic osteoarthropathy, is a rare disorder that may present with inflammatory arthritis and systemic inflammation, occasionally mimicking rheumatologic disease. We report a male patient born in 1989 who underwent evaluation in Azerbaijan, Germany, and Turkey for long-standing joint symptoms and persistent inflammatory activity. Laboratory findings included elevated C-reactive protein and erythrocyte sedimentation rate, anemia, and hypergammaglobulinemia, while knee magnetic resonance imaging demonstrated synovitis, joint effusion, and bone marrow edema. Thoracic computed tomography abnormalities also required consideration of secondary hypertrophic osteoarthropathy. After insufficient response to etoricoxib and a tumor necrosis factor inhibitor, weekly subcutaneous tocilizumab 162 mg produced marked clinical and laboratory improvement within approximately six weeks. However, a flare of pre-existing furunculosis-like subcutaneous inflammatory lesions caused psychological distress and led to treatment discontinuation. This case highlights diagnostic and therapeutic complexity of inflammatory phenotypes within the pachydermoperiostosis/hypertrophic osteoarthropathy spectrum and emphasizes carefully monitoring cutaneous manifestations during biologic therapy.

Keywords: pachydermoperiostosis; hypertrophic osteoarthropathy; inflammatory arthritis; tocilizumab; furunculosis.

1 | Introduction

Pachydermoperiostosis, also known as primary hypertrophic osteoarthropathy, is a rare hereditary disease classically characterized by skin thickening, digital clubbing, and periostosis of the long bones. According to current understanding, one of the main mechanisms of the disease is related to impaired prostaglandin E2 metabolism; in particular, alterations in the HPGD and SLCO2A1 genes may lead to proliferative changes in bone, skin, and soft tissues [1].

However, the pachydermoperiostosis/hypertrophic osteoarthropathy spectrum is not limited to the classic skin-bone triad. Patients may present with increased sweating, thickening of the forehead and scalp, gyrate changes of the scalp, enlarged hands and feet, joint pain, joint effusion, and, in some cases, an active arthritis component. Because of this variable clinical presentation, the disease may be mistaken for rheumatoid arthritis, seronegative arthropathies, acromegaly, or paraneoplastic conditions [2].

The most important clinical issue within the hypertrophic osteoarthropathy spectrum is the proper distinction between primary and secondary forms. Since secondary hypertrophic osteoarthropathy may be associated with pulmonary, pleural, cardiac, hepatic, infectious, and malignant diseases, a systematic differential diagnostic approach is required when digital clubbing, osteoarticular pain, and periosteal changes are identified [3].

Regarding treatment, there is no standardized approach supported by a high level of

evidence for pachydermoperiostosis. In most cases, non-steroidal anti-inflammatory drugs are used for symptom control; in selected patients, clinical improvement has been reported with cyclooxygenase-2 inhibitors and bisphosphonates [4,5].

However, in some patients, the main problem is not limited to bone and skin changes but includes persistent systemic inflammation and an active arthritis component. In such cases, the pachydermoperiostosis/hypertrophic osteoarthropathy spectrum may be considered not only as a cosmetic or skeletal-cutaneous syndrome but also as an inflammatory phenotype requiring rheumatologic treatment decisions. Cases of clinical improvement with methotrexate in inflammatory variants have also been described in the literature [6].

In this context, the present case is noteworthy because it involves inflammatory arthritis, persistent systemic inflammation, differential diagnosis with secondary causes, and a biologic treatment dilemma within the pachydermoperiostosis/hypertrophic osteoarthropathy spectrum. The aim of this case is not to claim a definitive diagnosis, but to demonstrate how clinical decisions in such patients should be made in a stepwise, cautious, and multidisciplinary manner.

2 | Case presentation

A male patient born in 1989 was evaluated stepwise in Azerbaijan, Germany, and Turkey because of long-standing joint complaints, persistently elevated systemic inflammatory markers, and diagnostic uncertainty. Available records suggest that



the clinical concern was not limited to localized joint pain but rather involved a chronic systemic inflammatory process.

The earliest extensively documented evaluations were performed in Germany in December 2018 and January 2019. At this stage, elevated C-reactive protein, anemia, increased immunoglobulin levels, and an increased gamma fraction on serum protein electrophoresis were documented. Across different records, C-reactive protein was 23.3–27.9 mg/L, hemoglobin was approximately 10.9 g/dL, immunoglobulin G was 27.1–31.2 g/L, and the gamma-globulin fraction was approximately 29–30%. Severe vitamin D deficiency was also recorded. No major abnormalities in liver or kidney function were observed.

Repeated laboratory testing performed in Azerbaijan in 2019 also showed persistent inflammatory activity. At this stage, anemia, elevated erythrocyte sedimentation rate, increased C-reactive protein, elevated immunoglobulin levels, and increased creatine kinase were recorded. The documents showed C-reactive protein at approximately 36.6 mg/L, creatine kinase at 453 U/L, and immunoglobulin G at 22.4 g/L. Anemia persisted on complete blood count, with hemoglobin ranging between 7.8 and 9.7 g/dL at certain time points. These results supported the presence of sustained systemic activity rather than an isolated episodic process.

During a broader evaluation performed in Turkey in July 2023, the inflammatory burden was more pronounced. Laboratory results showed hemoglobin of 7.6 g/dL, erythrocyte count of $2.89 \times 10^6/\mu\text{L}$,

hematocrit of 25.7%, erythrocyte sedimentation rate of 119 mm in the first hour and 140 mm in the second hour, and high-sensitivity C-reactive protein of 42.7 mg/L. The leukocyte count was recorded as $7,400/\mu\text{L}$ and the platelet count as $177 \times 10^3/\mu\text{L}$. At the same stage, total protein was 8.8 g/dL, albumin 4.6 g/dL, globulin 4.0 g/dL, the albumin/globulin ratio was 0.9, and rheumatoid factor was 93.9 IU/mL. These findings were interpreted as consistent with ongoing systemic inflammation, anemia of chronic inflammation, and immunologic activity.

Radiologic assessment is presented based on formal reports because full access to the original radiologic images and DICOM files was not available. The chest computed tomography report described bilateral pleural effusion, infiltrative changes in the lung parenchyma, and a left-sided subpleural solid nodule. These findings made it necessary to consider the possibility of secondary hypertrophic osteoarthropathy and prevented the diagnostic approach from being limited to a purely rheumatologic framework.

The contrast-enhanced left knee magnetic resonance imaging report performed during the same period described bone marrow edema in the distal femur, proximal tibia, and fibula, increased intra-articular fluid, synovial thickening, and synovitis. These findings provided objective evidence of an active arthritis component in the patient. Additional documents included electrocardiography, echocardiographic images, and a bone marrow aspiration result; the bone marrow was described as normocellular.



One diagnostically notable point was the presence of the note “pachydermoperiostosis with arthritis” in a clinical document related to methotrexate. The presence of patient information forms for methotrexate and leflunomide also indicated that disease-modifying rheumatologic therapies had been considered. However, because the exact start dates, doses, treatment durations, and objective response measures for these medications could not be consistently traced in the records, this part is presented cautiously and based only on documented information.

In the subsequent treatment phase, etoricoxib was used first, but an adequate clinical and laboratory response was not achieved. Biological treatment with a tumor necrosis factor inhibitor was then administered; after six injections, no meaningful response was observed, and the treatment strategy was changed again. Because of persistently elevated C-reactive protein, erythrocyte sedimentation rate, anemia related to chronic inflammation, and systemic activity, the interleukin-6 pathway was considered to possibly play a major role, and tocilizumab was initiated at a weekly subcutaneous dose of 162 mg. Within approximately six weeks, inflammatory markers and hematologic abnormalities improved, while the patient reported an approximately 90% reduction in joint and systemic symptoms.

However, despite improvement in systemic and joint manifestations, the patient experienced a flare of previously existing large subcutaneous inflammatory lesions with a furunculosis-like appearance. The lesions were described in the available

records as large inflammatory subcutaneous lesions rather than microbiologically confirmed furuncles. This cutaneous process was physically, cosmetically, and psychologically burdensome for the patient. Because of the limitations of retrospective data, it was not possible to definitively determine whether this cutaneous flare represented activation of the underlying cutaneous component of the disease, an infectious complication under interleukin-6 blockade, or a paradoxical drug-related cutaneous reaction. As a result, the patient discontinued treatment because of the psychological burden.

Overall, the available data indicate a complex clinical picture characterized by long-standing systemic inflammation, an active arthritis component, anemia, immunologic activity, consideration of secondary causes because of thoracic findings, and stepwise biologic treatment decisions. The case is presented not as genetically confirmed pachydermoperiostosis but as an inflammatory phenotype and therapeutic dilemma within the pachydermoperiostosis/hypertrophic osteoarthropathy spectrum.

3 | Discussion

The pachydermoperiostosis/hypertrophic osteoarthropathy spectrum is classically associated with skin thickening, digital clubbing, and periostosis of the long bones; however, these findings are not always present simultaneously or completely in clinical practice. When joint pain, swelling, synovitis, and elevated inflammatory markers predominate, the condition may



mimic inflammatory rheumatologic diseases [7,8].

The present case illustrates this inflammatory phenotype. Objective evidence of synovitis, increased intra-articular fluid, and bone marrow edema on left knee magnetic resonance imaging, together with persistent systemic inflammatory activity, supported the presence of an active inflammatory articular component rather than solely mechanical or periosteal symptoms [9,10].

An important diagnostic issue was the distinction between primary and secondary hypertrophic osteoarthropathy. The reported bilateral pleural effusion, infiltrative pulmonary changes, and subpleural solid nodule required consideration of pulmonary secondary causes. Accordingly, it is more appropriate to describe this case as a diagnostic and therapeutic dilemma within the pachydermoperiostosis/hypertrophic osteoarthropathy spectrum rather than as genetically confirmed pachydermoperiostosis [11].

From a radiologic perspective, the available information is based on formal reports because full access to the original radiologic images and DICOM files was not possible. Since classical long-bone radiographs were not available, periostosis could not be directly demonstrated. Nevertheless, the reported active synovitis and bone marrow edema on knee magnetic resonance imaging provided objective support for an inflammatory articular component. This represents an important limitation of the retrospective, multi-country nature of the case.

There is no standardized treatment algorithm for the pachydermoperiostosis/hypertrophic osteoarthropathy spectrum supported by a high level of evidence. Non-steroidal anti-inflammatory drugs and, in selected patients, cyclooxygenase-2 inhibitors and bisphosphonates are generally used for symptom control [12,13]. However, when inflammatory arthritis and elevated acute-phase reactants are prominent, symptomatic treatment alone may be insufficient. Clinical improvement with methotrexate and biologic approaches has been reported in selected inflammatory phenotypes [9,14].

In the present patient, the lack of meaningful response to etoricoxib and a tumor necrosis factor inhibitor was followed by marked improvement after the initiation of weekly subcutaneous tocilizumab. This response does not indicate that tocilizumab should be considered a standard treatment for this condition. Rather, it represents a clinical observation suggesting that individualized biologic treatment may have a role in selected patients with prominent inflammatory manifestations [15].

An important feature of this case was the worsening of cutaneous manifestations despite systemic and articular improvement. The patient had previously existing large subcutaneous inflammatory lesions with a furunculosis-like appearance, which became more prominent during tocilizumab treatment. Because bacterial culture or biopsy of these lesions was not performed, they cannot be classified definitively as infectious furunculosis. It also remains unclear whether the flare reflected the underlying cutaneous component of the



disease, an infection occurring during interleukin-6 blockade, or a paradoxical drug-related reaction.

The case therefore emphasizes that laboratory and articular improvement does not necessarily indicate complete disease control. Although inflammatory markers and joint symptoms improved, the cutaneous flare caused significant psychological distress and ultimately led to treatment discontinuation. Treatment response in such patients should therefore be assessed not only through C-reactive protein, erythrocyte sedimentation rate, complete blood count, and joint symptoms but also through cutaneous manifestations, daily functioning, cosmetic concerns, psychological burden, and treatment adherence. In patients considered for biologic therapy, baseline dermatologic findings should be documented and potential infectious and cutaneous complications should be taken into account.

Limitations: This case is based on retrospective and multi-country medical documentation; therefore, full access to some data was not possible. Because original radiologic images and DICOM files were not available, imaging findings were presented based on formal radiology reports. The exact onset date of symptoms and whether digital clubbing, skin thickening, scalp changes, and hyperhidrosis were present on the initial physical examination were not fully documented. Classical long-bone radiographs, HPGD/SLCO2A1 genetic testing, and bacterial culture or biopsy results during the cutaneous flare were not available. Nevertheless, the available clinical, laboratory, radiology-report, and treatment

data allow the case to be presented as a diagnostic and therapeutic dilemma within the pachydermoperiostosis/hypertrophic osteoarthropathy spectrum.

5 | Conclusion

This case demonstrates that the pachydermoperiostosis/hypertrophic osteoarthropathy spectrum may present not only with the classic skin-bone triad but also with active inflammatory arthritis, persistent systemic inflammation, and difficult treatment decisions. Although short-term clinical and laboratory improvement was achieved with tocilizumab after non-response to a tumor necrosis factor inhibitor, the furunculosis-like cutaneous flare impaired the patient's treatment adherence. The main lesson of this case is that successful control of systemic inflammation in such patients does not necessarily mean that cutaneous disease, psychological burden, and patient satisfaction are also under control.

Ethical statement

This case report was prepared in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from the patient for the scientific and anonymized publication of clinical information. Information that could identify the patient was removed from the manuscript.

Author contributions

All authors contributed to the clinical evaluation of the case, data collection, interpretation of findings, manuscript preparation, and approval of the final version. All authors read the final version of the manuscript and agreed to its submission.



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Conflict of interest

The authors declare that they have no conflicts of interest.

Data availability

The data supporting this case report may be obtained from the corresponding author upon reasonable request, provided that patient confidentiality is protected.

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