PAPA Syndrome: Challenges in Achieving Long-Term Remission

For over two decades, the acronym PAPA syndrome has been used to describe an autoinflammatory condition caused by missense mutations in the PSTPIP1 (proline-serine-threonine phosphatase interacting protein 1) gene and clinically characterized by the presence of pyogenic arthritis, pyoderma gangrenosum (PG), and acne (1,2).

Due to the involvement of the PSTPIP1 gene in the regulation of innate immunity, mutations of this gene cause abnormal activation of inflammasomes, complexes of NLRP3/ASC/caspase-1 proteins. As a result, production of interleukin-1β, a key molecule that triggers synthesis of cytokines necessary for the recruitment of neutrophils, is significantly increased (2,3). Additionally, the levels of other pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interferon-γ (INF-γ) and interleukin 17 (IL-7) are also elevated, which further disrupts inflammatory mechanisms in the microenvironment (4). Since hyperproduction of IL-1 and other involved cytokines is the predominant event in the pathogenesis, these molecules are promising targets in the treatment of PAPA syndrome.

Corticosteroids and biologics are currently the most commonly used agents for inducing and hastening remission of symptoms (5). A substantial step forward in the treatment of PAPA syndrome has been the introduction of medications blocking the cytokines crucial in the pathogenesis of this disorder, with TNF-α and IL-1 inhibitors being the most frequent choice of such biological therapy (6).

We report the case of a 22-year-old male patient with PAPA syndrome who was referred to our department 18 months ago due to exacerbation of skin changes. Initial presentation and subsequent evolution of disease in this patient matched the typical clinical pattern of PAPA syndrome. The first symptoms occurred at the age of two in the form of unspecific joint disease that was diagnosed as juvenile idiopathic arthritis. Subsequently, in the early adolescence the patient presented with new skin changes manifesting as severe acne and persistent pyoderma gangrenosum-like ulcers. At the same time, severity of joint involvement gradually decreased. After the characteristic phenotype of the disease had fully developed, suspicion of possible syndromic origin of symptoms arose. For this reason, genetic analysis was performed as requested by attending pediatricians at the University Clinical Center in Sarajevo, and E250Q mutation of the PSTPIP1 gene was detected. Thus, the diagnosis of PAPA syndrome was confirmed.

Throughout the duration of the disease, several types of medication had been introduced in the treatment with varying success. Earliest joint symptoms were alleviated with non-steroidal anti-inflammatory drugs, while repeated courses of corticosteroids were the mainstay of the therapy during a decade-long period. As a consequence of prolonged steroid therapy, growth disorder, among various other side-effects, had been especially pronounced. Acting as a classic steroid-sparing immunosuppressive agent, methotrexate had also been part of the patient's treatment regimen. Lastly, biologics, including both TNF-α and IL-a inhibitors, had been separately administered as the remaining treatment options. However, adalimumab expressed a predominant effect on joint symptoms, whereas re-activation of previously undetected Hepatitis-B infection occurred during the subsequent therapy with anakinra. Due to this adverse reaction, anakinra treatment was discontinued.

At the initial examination, the patient presented with multiple erythematous, partially excoriated papules and nodules, along with residual post-inflammatory hyperpigmented patches and scars on the skin of the whole back, chest, shoulders, and upper arms (Figure 1, Figure 2). The presence of postoperative scars on the elbows, resulting from previously performed surgical procedures of persistently affected joints with the goal of achieving pain relief and functional improvement, was also observed. Several smaller ulcers with undermined edges (Figure 3), as well as residual hyperpigmentation and cicatrices

(Figure 4) were visible on the lower extremities. Additionally, the patient reported appearance of pustules and non-healing ulcers after minor trauma, which corresponds to the pathergy phenomenon, a common feature of PAPA syndrome. In contrast to the severity of cutaneous changes, the joint symptoms were mild.

After thorough assessment of the patient's medical history and current condition, a multi-agent regimen was initiated, consisting of adalimumab, isotretinoin, and prednisone. Regular check-ups during the 12 months of treatment showed that the applied agents stabilized the patient's condition, alleviated more severe and acute skin changes, and slowed down further exacerbation of symptoms.

Due to the rarity of PAPA syndrome, data on its treatment is scarce. Official guidelines are non-existing, and available information is based on case reports, case series, and a few smaller retrospective studies (5,7). In general, response to therapy remains inconsistent between patients, despite introduction of novel drugs. Furthermore, single treatment regimens are often not equally effective for all manifestations of the disease, which in a number of cases results in the administration of multi-agent treatment (2). As described in our case report, we opted for a multi-agent regimen not only due to specific individual role of each drug in the treatment of PAPA syndrome but also because of the possible augmented effect of combined therapy. Initially, a short course of systemic corticosteroid (prednisone 30 mg/day for 3 weeks) was introduced in order to alleviate acute symptoms until other agents started showing their effects. The initial dose of administered corticosteroid was gradually tapered by 5 mg every week and soon discontinued. Adalimumab (40 mg every 2 weeks for 12 months) was chosen since its previous administration was without significant adverse effects and with more acceptable end results, unlike therapy with anakinra (8). In addition, TNF-α inhibitors, such as adalimumab, etanercept, and infliximab, have been generally regarded as a more effective treatment option for cutaneous changes, while anakinra, an anti-IL-1 agent, has been more beneficial in alleviating joint symptoms (9-11). Since the skin of our patient was significantly more affected than the joints, adalimumab was a preferred option for biological treatment. Finally, isotretinoin (0.5 mg/kg/day for 6 months) also found a place in our multi-agent therapy plan as a specific, supportive treatment agent for acne (12). Due to the fact that our national health insurance system covered the costs of treatment with TNF-α inhibitors for only 12 months, adalimumab had to be discontinued after the end of this period. Episodes of acute exacerbation that the patient experienced after the cessation of multi-agent regimen were addressed with systemic corticosteroids and symptomatic therapy.

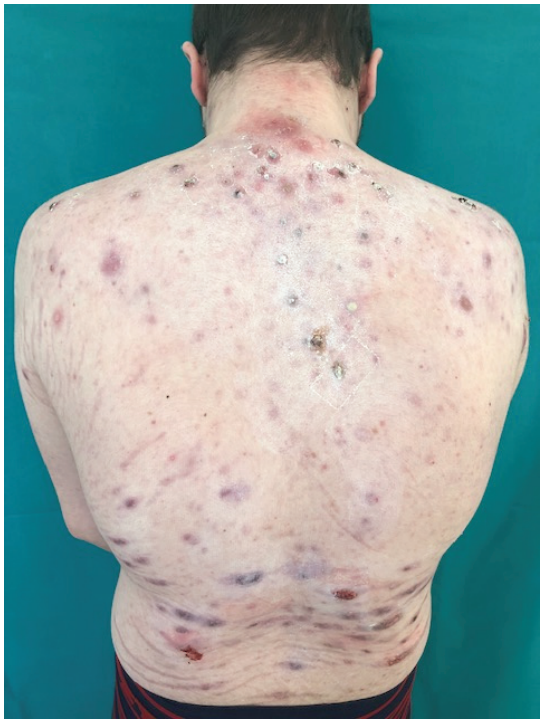

Figure 1. Multiple erythematous and partially excoriated papules and nodules, along with residual, postinflammatory hyperpigmented patches and scars on the back.

Based on case reports, corticosteroids are usually one of the first agents to be administered in patients diagnosed with PAPA syndrome. They are frequently effective in alleviating joint symptoms, but, on the other hand, high doses of corticosteroids can worsen acne lesions (6). Moreover, due to the multiple

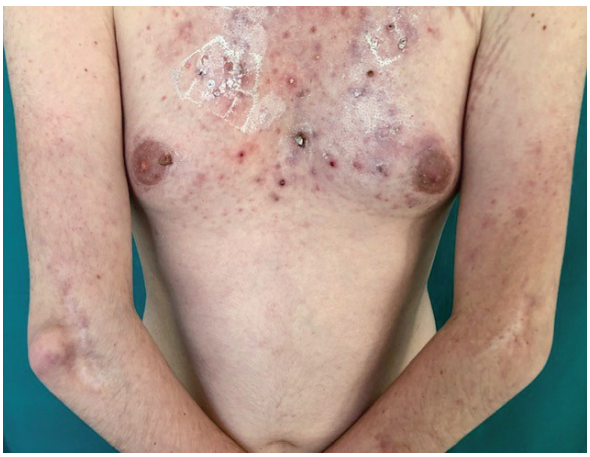

Figure 2. Multiple erythematous and partially excoriated papules and nodules, along with residual postinflammatory, hyperpigmented patches on the chest and upper extremities. Postoperative scars on both elbows.

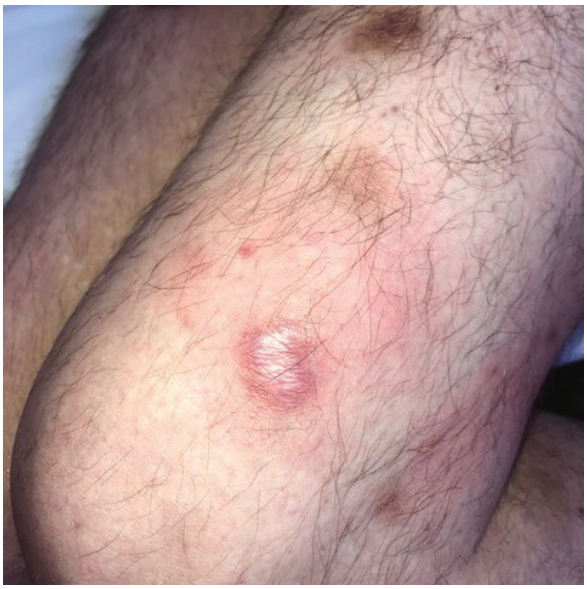

Figure 3. Ulcer on the lower extremities.

side-effects of corticosteroids, such as electrolyte abnormalities, hypertension, hyperglycemia, osteoporosis, growth suppression, and adrenal insufficiency (13), a steroid-sparing agent is typically introduced into treatment together with or after corticosteroid therapy.

A substantial step forward in the treatment of PAPA syndrome has been achieved with the introduction of medications targeting cytokines crucial in the pathogenesis of this disorder. The two most commonly used groups of such biological drugs have been those that block TNF-α and IL-1. A longer lasting improvement of symptoms has been achieved in a number of cases with both types of agents. Since other medications have often failed to establish long-term control of PAPA syndrome, such effects can be seen as a valuable accomplishment (6,14). Regardless of this observation, the response to treatment still differs between patients. More variable effects have been documented for IL-1 inhibitors, such as anakinra, while TNF-α inhibitors, such as adalimumab, infliximab, and etanercept, have been associated with more steady responses (4,6,10). The inconsistent effect of biologic therapies could be explained by the fact that PSTPIP1 protein is involved in various biochemical processes in different cells of the immune system. Thuse, none of the medications has an adequate spectrum of activity to control all involved immunological pathways (5,15).

Overall, due to scarcity of valid information and guidelines, there is an increasing need for multicentric randomized controlled trials that would provide evidence-based data on effective treatment options for PAPA syndrome. Despite the rarity of this disorder,

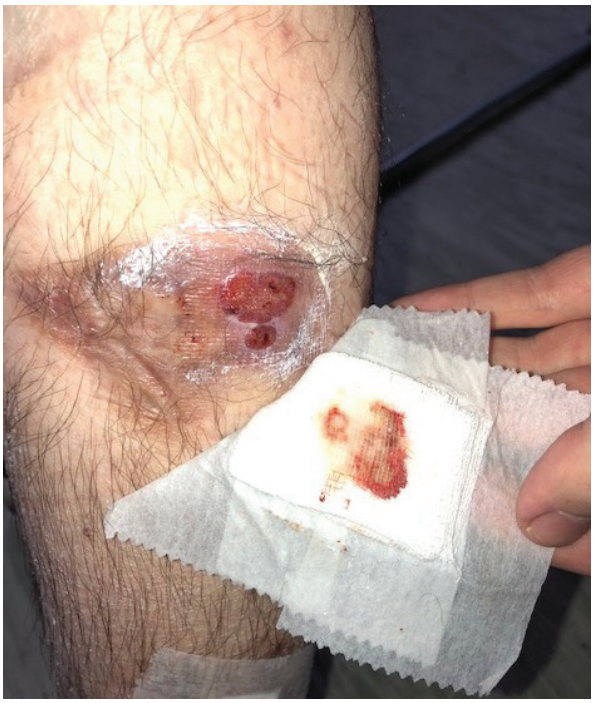

Figure 4. Residual hyperpigmented and scars on the lower extremities.

extensive research should be performed in order to discover therapies that could successfully manage all different manifestations of PAPA syndrome. Consequently, such efforts and breakthroughs would lead to decreased mortality and improved quality of life for patients suffering from this debilitating disease.

The case described herein shows that PAPA syndrome can remain undiagnosed for longer periods of time, resulting in delayed treatment. Furthermore, the available therapeutic options are not sufficient to achieve long-term remission in many patients. Thus, continuous and comprehensive research is vital for ensuring adequate care of patients with PAPA syndrome.

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