INTRODUCTION

Since the late 1990s, tumor necrosis factor (TNF-α)-alpha inhibitors (TNFi) have been successfully employed in the treatment of many inflammatory disorders, such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), Crohn’s disease (CD), psoriasis and psoriatic arthritis (PsA) (1). With the increased use of TNFi, several adverse events have been reported such as infections, cancers and skin reactions (2, 3). Among the latter, new-onset or exacerbated psoriatic lesions have been described in a number of patients while on TNFi (3-6). These lesions can be considered a paradoxical event, given that TNFi are successfully used in the treatment of psoriasis (1).

In this case report, we describe a patient with AS who developed severe palmo-plantar pustulosis (PPP) after treatment with infliximab, which led to the discontinuation of the TNFi. PPP was non-responsive to both local and systemic therapies, and the interruption of infliximab resulted in a severe flare of AS. The employment of ustekinumab led to a rapid and persistent remission of both PPP and SA. Review of the literature was focused on the identification of cases of PPP without concomitant psoriasis developed after TNF-α-inhibitors. Main pathogenetic mechanisms that link the appearance of PPP to the use of TNFi and the difficulties in PPP treatment are discussed.

CASE REPORT

A 37-year-old Moroccan man presented at our outpatient clinic in May 2014 complaining of inflammatory low back pain, alternate buttock pain and prolonged morning stiffness (>2 hours).

Back pain had begun about five years earlier as a continuous dull pain with mainly mechanical characteristics, so it was considered a result of patient’s job (bricklayer). Because of the persistence of pain, in 2010 the orthopedic presribed MRI of the lumbar spine, which showed the presence of mild degenerative changes in the absence of inflammatory signs. Physiotherapy and short cycles of NSAIDs were prescribed with partial benefits. From 2012 to 2014 the pain became predominantly inflammatory so the patient was taking NSAIDs almost daily. His medical history was unremarkable and he had no family history of rheumatic or skin diseases.

On physical examination, a limitation of his lumbar spine flexion (Schober index=10+3cm, finger-to-ground distance=9 cm) was evidenced. BASDAI and BASFI resulted 7.2 and 6.6, respectively. No clinical signs of synovitis, enthesitis or psoriasis were appreciable. Laboratory tests showed increased erythrocyte sedimentation rate (ESR) (46 mm/hour) and C-reactive protein (CRP) (19 mg/L). X-rays of the lumbar spine and pelvis showed bilateral sacroiliitis with erosions (Figure 1A). Magnetic resonance imaging (MRI) of the sacroiliac joints and lumbar spine evidenced the presence of bone marrow edema on both sides of sacroiliac joints and synovitis on the right side with no signs of inflammation of the vertebral bodies (Figure 1B).

Figure 1. A: X-Ray examination of sacroiliac joints. Bilateral sclerosis (head arrows), small erosions (arrow) and poor definition of sacroiliac joints. B: MR examination of sacroiliac joints. Coronal T2-STIR. High signal intensity on both sides of sacroiliac joints (bone marrow edema: head arrows) and synovitis on the right side (arrow).

HLA-B27 resulted positive. According to modified New York criteria (7) the diagnosis of AS was established. The patient started Infliximab in July 2014 at a dose of 5 mg/kg following usual scheduled protocol (0-2-6 and then every 8 weeks). At the end of the first 3 doses, the patient experienced complete remission of pain, with normalization of ESR (12 mm/hour) and CRP (1.1 mg/L) and without drug related side effects. BASDAI and BASFI dropped to 2.4 and 2.8, respectively. In October 2014, forty-five days after third infusion, the patient developed an acute PPP with no other signs of psoriasis appreciable in local and systemic therapies, and shortly after discontinuation of TNFi the patient experienced a severe flare of AS, poorly responsive to the administration of non-steroidal anti-inflammatory drugs. Ustekinumab led to a rapid and persistent remission of both PPP and SA. Review of the literature was focused on the identification of cases of PPP without concomitant psoriasis developed after TNF-α-inhibitors. Main pathogenetic mechanisms that link the appearance of PPP to the use of TNFi and the difficulties in PPP treatment are discussed.

REFERENCES

1. New onset or exacerbated psoriatic lesions in patients treated with TNF-α-inhibitors (TNFi) have been frequently reported in literature. We describe a patient with ankylosing spondylitis (AS) who developed a very severe palmo-plantar pustulosis (PPP) after the third infusion of infliximab, whose administration was consequently stopped. PPP was refractory to both local and systemic therapies, and shortly after discontinuation of TNFi the patient experienced a severe flare of AS, poorly responsive to the administration of non-steroidal anti-inflammatory drugs. Ustekinumab led to a rapid and persistent remission of both PPP and SA. Review of the literature was focused on the identification of cases of PPP without concomitant psoriasis developed after TNF-α-inhibitors. Main pathogenetic mechanisms that link the appearance of PPP to the use of TNFi and the difficulties in PPP treatment are discussed.

KEYWORDS : palmo-plantar pustulosis, TNF-α inhibitors, ankylosing spondylitis, ustekinumab
and buttock pain, prolonged morning stiffness and new onset inflammatory dorsal pain. Acute phase reactants were increased (ESR: 52 mm/hour; CRP: 21 mg/L). BASDAI and BASFI were 7.5 and 6.3, respectively. Because of both PPP and AS, the patient was not able to carry out his job. MRI of the spine showed signs of active spondylitis with bone marrow edema in four vertebral bodies of the dorsal spine (D8-D11) (Figure 2,3) and the persistence of bilateral active sacroiliits (Figure 4), with no signs of inflammation at the level of lumbar vertebral bodies.

Six months later, in addition to resolution of PPP, a clinical (BASDAI:2.4; BASFI:2.2) and laboratory (ESR: 10 mm/hour; CRP: 6.5 mg/L) resolution of AS were evidenced. Again, twelve months later, BASDAI and BASFI were 2.4 and 2.2, respectively. Because of both PPP and AS, the patient was not able to carry out his job. MRI of the spine evidenced a complete resolution of the dorsal inflammatory lesions (Figure 5). At the level of sacroiliac joints, a mild reduction of bone marrow edema especially on the sacral side and resolution of synovitis were highlighted (Figure 6).

Figure 2: MR examination of dorsal spine. Sagittal T1. Low signal intensity of anterior corners (D8-D9) related to bone marrow edema (arrows)

Figure 3: MR examination of dorsal spine. Sagittal T2-STIR. High signal intensity of opposing anterior corners (D9-D10) (arrows), anterior-inferior corners (D8-D10-D11) (head arrows) and opposing posterior corners (D4-D5) (stars) related to bone marrow edema.

Figure 4: MR examination of sacroiliac joints. Coronal T2-STIR. High signal intensity on both sides of SI joints (bone marrow edema: head arrows) and synovitis on right sacroiliac joint (arrow).

Between January and March 2015, the patient was treated with NSAIDs with only partial benefit. Moreover, PPP worsened even more so treatment with systemic corticosteroids was started with only limited benefits. In April 2015, ustekinumab was available in Italy and it was started at the dosage of 45 mg subcutaneously, followed by a dose of 45 mg after 4 weeks and, subsequently, every 12 weeks. Thirty days after the first injection, PPP resulted completely resolved but symptoms of AS persisted. After sixty days, complete resolution of PPP was confirmed, and a good control of pain and stiffness (BASDAI: 4.1; BASFI: 4.6) with reduction of acute phase reactants (ESR: 25 mm/hour; CRP: 6.5 mg/L) were recorded.

Six months later, in addition to resolution of PPP, a clinical (BASDAI:2.4; BASFI:2.2) and laboratory (ESR: 10 mm/hour; CRP: 3 mg/L) remission of AS were evidenced. Again, twelve months later, resolution of PPP and clinical and laboratory remission of AS still persisted. MRI of the spine evidenced a complete resolution of the bone marrow edema (arrows) and synovitis on right sacroiliac joint (Figure 5).

Figure 5: MR examination of dorsal spine. Sagittal T2-STIR. Complete resolution of the bone marrow edema.

DISCUSSION

PPP is an inflammatory skin condition of unknown origin localized to the palms and soles, involving intra-epidermal part of the eccrine sweat glands and characterized by a chronic, relapsing eruption of sterile pustules leading to hyperkeratosis, erythema, and fissuring (8, 9). To date it is unclear whether it is a distinct entity or a localized pustular variant of psoriasis, since coexistent psoriasis has been reported in 24% of patients with PPP (10). However, PPP is usually distinguished from the palmo-plantar pustular psoriasis (PPP) as suggested by clinical, histopathological and genetic data (8, 11, 12).

New-onset or exacerbated psoriatic lesions secondary to TNFi, including PPP and PPPP, have been described up to date in many patients. The first reported was a case of psoriasis induced by infliximab in a patient with Crohn’s disease (13). Recently, Cicccarelli et. al published a complete comprehensive review of literature about psoriasis induced by TNFi (1). Taking hint from our case, we focused our review on the identification of cases of PPP without concomitant psoriasis induced by TNFi. Literature search yielded 32 papers which satisfied pre-defined inclusion criteria (Table 1), corresponding to fifty five cases of pure PPP: 50 with the involvement of palps and soles, 4 with only plantar lesions and 1 with palmar lesions, alone. Twenty-three patients had received TNFi because of RA, 7 inflammatory bowel diseases (CD and ulcerative colitis), 6 psoriasis, 4 SAPHO (Synovitis Acne Pustolosis, Hyperostosis, Osteomyelitis) syndrome, 3 spondiloarthritides (SpA) and 1 PsA.

| Table 1 Palmo-plantar pustulosis developed after TNFi |
|-----------------|-----------------|-----------------|
| Author          | Year            | Disease         | TNFi            |
| Baeten et al (30)| 2005            | SpA             | Infliximab      |
| Jarrett et al (31)| 2003           | RA              | Infliximab      |
| Haibel et al (32)| 2004           | AS              | Infliximab      |
|                 |                 |                 | Etanercept      |
| Zarnitsky et al (33)| 2004 | RA              | Adalimumab      |
| Sturman-Koel et al (34)| 2005 | AS              | Infliximab      |
| Pirard et al (35)| 2006           | AS              | Infliximab      |
| Kary et al (36)  | 2006            | RA              | Etanercept      |
| Massara et al (37)| 2006           | SAPHO           | Infliximab      |
| Goncalves et al (38)| 2006| AS              | Infliximab      |
| Gonzalez-Lopez et al (39)| 2006| AS              | Adalimumab      |
| Goiriz et al (40) | 2006            | RA              | Infliximab      |
| Ubirani et al (41)| 2007           | RA              | Adalimumab      |
Th17 cells besides having various additional functions (25-27). A number of effects in immune regulation, IL-23 is the key stimulator that ustekinumab may represent at least in PPP induced by TNFi. The antibody targeting the p40 subunit shared by interleukin-12 (IL-12) and IL-23, for new treatments has led to employ ustekinumab, an antibody targeting the p40 subunit common to IL-12 and IL-23, it has also been shown that TNFα blockade may lead to IFNα over-expression with consequent onset of psoriasis (15). According to another hypothesis TNFi may induce a disruption of the immune pathways are also potential key players (1). PPP and PPPP have been described both with classical Spondylitis; PsA: Psoriatic arthritis

| Table 1 legend: RA: Rheumatoid arthritis; AS: Ankylosing spondylitis; IBD: inflammatory bowel diseases; SAPHO: Synovitis, Acne, Pustulosis, Hyperostosis, Osteomyelitis; SpA: Spondyloarthritis; PsA: Psoriatic arthritis

No significant predisposing factors to these paradoxical reactions have yet been identified, but it is likely that genetic susceptibility could have a role (1). PPP and PPPP have been described both with classical (infliximab, adalimumab, etanercept) and new (certolizumab, golimumab), which suggests a class effect rather than a drug-specific effect (1, 14). The pathogenetic mechanism is not fully known and several theories have been proposed. One of the most intriguing hypotheses suggests that TNFα blockade may lead to IFNα over-expression with consequent onset of psoriasis (15). According to another hypothesis TNFi may induce a disruption of the immune system equilibrium, enhancing Th1 function and down-regulating Th2-reg expansion (16). However, it may be that other cytokine and T-cell pathways are also potential key players (1).

Treatment of both PPP and PPPP is a clinical challenge because these conditions are often refractory to both local and systemic therapies. Ustekinumab, an antibody targeting the p40 subunit common to IL-12 and IL-23, may be effective, as at least in PPP induced by TNFi an antibody targeting the p40 subunit common to IL-12 and IL-23 has been tested in TNFα-naive active AS patients in the TOPAS study, a prospective open-label proof-of-concept study, and an ASAS 40 response was reached in 65% of the patients, a BASDAI 50 response in 55% and ASAS partial remission in 30% of patients (29). In our patient ustekinumab led to a clinical and laboratory rapid and persistent remission. In addition, MRI evidenced a complete resolution of the dorsal inflammatory lesions, while at the level of the sacroiliac joints inflammatory lesions remained stationary, and no signs of evolution were evidenced. However, sacroiliac joints in our patient were the first joints to be affected, while inflammatory lesions detected in the lumbar and thoracic spine were more recent. Although a surgical point of view, one may speculate that the early use of the drug is essential in reversing the inflammatory bone edema. The execution of the response after further 12 months will help to clarify this issue.

CONCLUSIONS
New-onset or exacerbated psoriatic lesions including PPP and PPPP have been described in many patients while on TNFi. Treatment of these conditions is a clinical challenge because they are often refractory to both local and systemic therapies. Ustekinumab, an antibody targeting the p40 subunit common to IL-12 and IL-23, may be effective, as at least in PPP induced by TNFi an antibody targeting the p40 subunit common to IL-12 and IL-23, may be effective, as at least in PPP induced by TNFi a valuable therapeutic option to control skin lesions. Ustekinumab was also effective in the treatment of AS, leading to a complete clinical and laboratory rapid and persistent remission. In addition, MRI evidenced a complete resolution of the dorsal inflammatory lesions, while at the level of the sacroiliac joints inflammatory lesions remained stationary, and no signs of evolution were evidenced. However, sacroiliac joints in our patient were the first joints to be affected, while inflammatory lesions detected in the lumbar and thoracic spine were more recent. Although a surgical point of view, one may speculate that the early use of the drug is essential in reversing the inflammatory bone edema. The execution of the response after further 12 months will help to clarify this issue.

REFERENCES


