ABSTRACT:
Background: One of the most common complications in psoriasis is the development of secondary gout that often remains undiagnosed for many years. In some cases, the clinical symptoms of gout precede the manifestation of cutaneous psoriasis, leading to progression of the disease and early onset of complications. According to the world data, there is a strong correlation between psoriasis vulgaris and psoriatic arthritis on the one hand and gout on the other ranging from 3 to 40%. In Bulgaria, there are no studies observing the frequency of secondary gout in psoriatic patients.

Purpose: We present 3 patients with psoriatic arthritis first misdiagnosed like gout.

Results: Due to the diagnostic mistake, the disease is active despite the optimal urate-lowering therapy. When initiating the underlying antirheumatic therapy for psoriatic arthritis, patient’s attacks and the number of tophi starts to decrease and uric acid levels remain stable in reference values.

Conclusion: These three case reports reveal the difficult differentiation of the types of arthritis and the importance of correct diagnosis in order to optimize the therapy and reduce the risk of developing complications that leads to increased mortality of the patients.

Keywords: Psoriasis, Psoriatic arthritis, Secondary gout

INTRODUCTION:
Psoriasis vulgaris (PV) is a complex, multifocal, chronic disease, due to genetic polymorphism (HLA B 16; 17; 27, 39) [1]. There is a presence of family history among close relatives. It is known that environmental factors, lifestyle, use of certain medications, trauma and infections can unlock the disease. According to the World health organisation (WHO) report of 2016, epidemiological spread of skin psoriasis in different countries varies from 0.09% to 11.4% [2, 3]; for Caucasians rate is about 3.6%, for Europe and America – 0.02 to 0.42% [4] considered that an earlier onset of the disease predicts more severe course. It is estimated that up to 69% of patients may develop nail changes associated with the disease [5].

The pathogenic mechanism in psoriasis is induced mainly by T cells in the dermis. The antigen-presenting cells in the skin (Langerhans cells) migrate to the regional lymph nodes, where interacts with T-lymphocytes. This provokes the immune response leading to the activation of T cells and release of cytokines. The local effects of cytokines lead to a cell-mediated immune response. In psoriasis skin lesions are results of hyperplasia of the epidermis, which leads to enhanced cell reproduction, hyperproliferation and at the same time shortening keratinocytes’ life. This leads to increased production of uric acid, as it enhances the exchange of nucleic acids.

Psoriatic arthritis (PsA) occurs in 0.05 to 0.25% from the general population. In patients with psoriasis this frequency ranges from 1.6 to 34.7 % globally; most often affects Caucasians – at about 20%. Usually the skin involvement precedes arthritis, but up to 18 % of the cases joint involvement precedes the skin manifestations [6]. Predominant antigen for patients with PsA „sine Psoriasis“ with family history is HLA Cw6, in those without – HLA B 27. It is considered that severe skin changes will predict a higher risk of aggressive arthritis and subsequent gout. It is considered that the risk of development of arthritis with the more aggressive course and of secondary gout is greater in patients with extensive skin involvement. There are typical radiological changes – asymmetric sacroiliitis, syndesmophytes, juxtaarticular new bone formation. Common changes are enthesitis (about 50%). This is a hallmark of seronegative spondyloarthropathies (psoriatic in particular) and the ultrasonographic evaluation contributes to differentiation of the types of arthritis – gout or psoriatic.

Gout (G) is an inflammatory crystal arthropathy caused by elevated levels of uric acid (UA) in the blood. It causes urinary acidic deposits in joints and the soft tissues, which leads to painful episodes of gouty induced arthritis. The condition can become chronic and can lead to severe joint damage as erosions, severe restriction of movement and disability.

Back in the 60’s the investigation of the establishment of hyperuricemia in a greater percentage than usual in patients with psoriasis and PsA. Arthur E. et al. prove by incorporation of isotopic uric acid, the presence of hyperuricemia in about 30 - 40% of patients with psoriasis and PsA. In primary gout, high levels of UA in the body are excreted through the urinary tract, while in the secondary it accumulates in the body as crystal deposits in the soft tissues, cartilage and internal organs [7].
Over the years, much less attention was paid to the link between these two diseases. In the recent decades this interest is growing, because of the relevance, differential diagnostic difficulties to differentiate them and to conduct an adequate treatment.

Coexistence of psoriasis vulgaris and gout is documented in several reports and cohort studies, but so far there are no prospective study of the relationship between psoriasis, PsA and the risk of secondary gout. In recent years, there has been significant interest in high-frequency musculoskeletal ultrasound in rheumatic diseases. This is due to the low cost, high reliability in experienced hands, and lack of contraindications on the part of the participants. Moreover, in the echography of rheumatic diseases, there are certain features that help to differentiate different kind of arthritis (enthesopathy in PsA, tophi, „snow storm” appearance, „double contour” sign in gout, erosions in Rheumatoid arthritis (RA), etc.). Therefore, it is particularly useful for establishing the diagnosis when it is difficult to precise. [8, 9, 10, 11]

Systemic review of the literature:

The interest in the relationship between PsA and secondary gout dates back to the 1930’s and continues to this day. There are many cohorts and case studies, with very controversial results. Herrmann [12], in 1930, reported that 44 (31.4%) of 140 patients with psoriasis had uric acid’ serum levels higher than 5 mg. This is observed mostly in patients with Psoriatic arthritis.

In 1952, Steinberg, Becker, Fitzpatrick, and Kierland [13] reported that 47 (48%) of 98 men and 19 (27%) of 74 women with Ps had elevated serum UA levels. Their criteria for hyperuricemia are values ≥6 mg. % or more in males and values ≥5 mg. % or higher in females.

In 1958, Lea, Curtis and Bernstein [14] reported that in a group of 17 psoriatic patients (9 women and 8 males) compared to a control group of 23 (7 women and 16 men) there is no significant difference in levels of the UA by urinalysis and UV spectrophotometric analysis, which the authors themselves consider non-specific and recommend further accurate examinations.

In 1960 Baumann [15] reported statistically significant differences in the measurement of UA levels between 76 males and females with psoriasis, and a control group of 68 subjects. The UA level in psoriatic patients was 5.73 ± 1.25; females - 4.4 ± 1.1 whereas in the control group the incidence varies between 4.7 ± 0.86 for males and females - 3.7 ± 0.75. Comparison between the two groups showed a high statistical significance of p = 2.18 in males and p = 2.60 in females. In the same year, Tickner and Mier [16] reported that 21% of 86 - psoriatic patients had UA levels greater than 5 mg, % and 4% have levels higher than 6.5 mg%. 2000, Bruce [17] conducted a cohort study to determine the relationship between the extent of skin involvement and UA levels in PsA patients conducted between 1991 and 1997. He proves that UA levels is elevated in 20% (55 out of 265 participants) of cases, as the relationship between UA levels and Psoriasis Area and Severity Index (PASI) is rejected. 2004 [18] Choi showed elevated UA levels associated with increased psoriasis activity. They also suggest that hyperuricemia is due to increased purine metabolism associated with accelerated epidermal decay. They report not only the relationship between the two diseases but also a higher incidence in psoriatic patients with already existing psoriatic arthritis.

In 2011, Kwon found a correlation between PASI in psoriatic patients with concomitant hyperuricemia until it found a statistically significant correlation by gender, disease age, or other laboratory values [19]

2012 [20] Lopez and all reported a case of a 34-year-old man with psoriasis with 22 years of a history of inflammatory back pain, tenderness in wrists, MCP, PIP joints of 6 years. Elevated values of CRP -10.8 mg/l Dl (<1.0 mg/dl) and UA 10.2 mg/dl (3.0-7.0 mg/dl) were found in the blood sample. MSU crystals are found in the synovial fluid after the arthrocentesis. The US examination if the I MTP joints found the presence of a double contour sign.

2013. Gisondi et al. [21] compared 119 patients with Ps and 119 healthy controls that matched age, gender, and BMI. They found that the UA level was 5.61 ± 1.6 on average compared to the control group, where the level was 4.87 ± 1.4 at (p<0.01). They also demonstrate that the incidence of asymptomatic hyperuricemia is 3 times higher in patients with Ps than in healthy controls (19% versus 7%).

Ashishkumar et al. [22] Reviewed 50 patients with psoriasis and 50 healthy controls to confirm or reject the relationship between hyperuricemia and psoriasis as well as the activity of skin disease and secondary UA levels. They found that there was no correlation between the hyperuricemia and PASI levels. In patients with PASI <10, the UA level was 5.46 ± 1.5 and those with PASI> 10 - 5.42 ± 2.2. In healthy controls the level of UA is 5.7 ± 0.57. The authors recognize the small number of patients as the main drawback of their study, giving as the main reason for hyperuricemia the feeding and genetic predisposition.

Merola et al all 2014 [23] conducted a study of 27,775 male and 7,109 female health workers from 1986 to 2010, who have psoriasis or PsA proven and evaluated with PASE (Psoriatic arthritis screening and evaluation). Of these, they report 2217 cases of Gout (according to American College of Rheumatology (ACR) 1977 classification criteria), which equate to 4.9% for men and 1.2% for women. In the multivariate analysis, the risk assessment was 1.79 (95% CI 1.30 to 2.47) in males and 1.63 (95% CI 1.17 to 2.27) in females and 1.71 (95% CI 1.36 to 2.15) in the combined analysis. In the additional analysis of patients with PV with complicated PsA, the risk assessment reached HR = 4.95, 95% CI 2.72 to 9.01) in the combined analysis.

CASE REPORTS

We report 3 cases of long-standing arthritis treated as chronic tophaceous gout. During the assessment of the patients we revealed characteristic signs for psoriatic arthritis according to CASPAR criteria for classification as PsA. Elevated UA values in all 3 patients were established in the context of late diagnosed PsA leading to keratinocyte hyperproliferation, intense purine degradation, and subsequently hyperproduction of UA.

**Medical history**: A 68-year-old patient with a diagnosis of gout over 18 years with multiple pain attacks with swelling in the small joints of the hands and feet, despite strict dietary control, NSAID and urate-lowering therapy. With a history of pain in the lumbosacral spine, shoulder joints, pelvis, hip and knee joints. History of “sausage” fingers accompanied by prolonged morning stiffness. 2 years ago with erythema rush on the elbows and knees. With progressive nail changes.

**Family history**: mother with psoriasis.

**Physical examination**: Erythema rush on the knees, elbows and squamous erythema rush on the head. Diffuse nail changes on the hands: pitting, onycholysis and Beau lines. Limited lumbar spine motions – Ott – 3.4 cm; Schober – 3.6 cm, decreased chest expansion, “sausage fingers”, pain in hip and knee joints. Physical data for sacroiliitis – Mennell sign (++).

**Laboratory**: Hb - 126 g/l; RBC – 4,31x10^{12}/l; WBC – 9,69x10^{12}/l; Plt - 242 g/l; CRP –12 mg/l; ESR – 44 mm/h; RF – 3 UI/ml; UA – 548 mmol/l; urine: 3 (+) protein; UA/24 h - 1,44 mmol.

**X-rays**: data for multiple syndesmophytes of the lumbal and thoracic spine, bilateral sacroiliitis gr. II-III. Arthrocentesis is not performed due to the patient’s background therapy with oral anticoagulant. **US findings**: thickening of the distal patellar tendon (enthesitis), typical double contour sign on the knees. (Fig. 1, 2, 3)

**QSK**

**Medical history**: A 66-years-old patient with long-lasting complaints begins at 25 years of age, with gouty-like attacks engaging small joints of the lower and upper limbs, subsequently with extension of the joint involvement and development of permanent deformities. Diagnosis gout was accepted with periodic treatment with urate-lowering therapy and NSAID’s with partial and temporary effect. With the appearance of erythema rash on the head, extensor surfaces of lower limbs at 40 years of age, the diagnosis PsA was established and initiation of basic therapy with Methotrexate 15 mg/weekly with a beneficial effect on the skin syndrome and joint complaints.

**Physical examination**: Reduced erythema rush on the head and upper and lower limbs, pitting on the nails of the both hands, tophi on the upper and lower limbs, limitation lumbar spine motions – Ott – 2 cm, Schober – 2,5 cm, decreased chest expansion, pain and synovitis of the wrists, MCP, PIP joints, flexion contracture of the right elbow, achillitis, sacroiliitis – Mennell (+), Faber (++).
Laboratory: Hb - 172 g/l; RBC – 4.87x10^{12}/l; WBC – 7.6x10^{12}/l; Plt - 207 g/l; CRP – 49 mg/l; ESR – 38 mm/h; UA – 547 mmol/l; 

X-rays: data for erosive changes with bone proliferation with a predominantly distal distribution in PIP joints, bilateral sacroilitis gr. III. Polarised microscopy after arthrocentesis – MSU crystals deposits. US findings: effusion in the two knees, synovitis on the MTP, PIP joints on the hands, presence of tophus on the 1 left MTP joint. (Fig. 4, 5, 6, 7.)

**Fig. 4.** Synovitis and effusion in the knee joint

**Fig. 5.** New bone formation in PIP joints

**Fig. 6.** Tophus

**Fig. 7.** US imaging of tophus in 1 MTP joint

AVK

Medical history: Debut of complaints in October 2011 with inflammatory pain, pronounced oedema and stiffness consistently in right knee and right ankle joints, occurring about a week after lacunar angina. Diagnosis Reactive arthritis was accepted, initiated therapy with salazopyrine (SSZ) with good response. Established hyperuricemia and the therapy with SSZ was discontinued, accepted diagnosis gout and started therapy with allopurinol for a few months without satisfactory effect. Consequently, due to the appearance of an erythema rash on the right foot and the head and the resumption of inflammatory joint syndrome accompanied by pronounced night pain and prolonged morning stiffness, accepted diagnosis PsA. Methotrexate therapy started with good response.

Family history: mother with gout.

Physical exam: Auricular and paraumbilical erythema rush, pitting scars on the nails, pain and synovitis on the knees and ankle and MTP joints. Effusion and synovitis in the knee joints. Limited lumbar spine motion – Ott


**CONCLUSION:**

The accepted features of gout – MSU crystals in synovial fluid, hyperuricemia, presence of tophi, establishing double contour, are often common findings in psoriatic arthritis and this creates differential diagnostic difficulties between the two diseases. The presence of sacroiliitis, entheseal involvement, new-bone formation on the hands and feet helps to classified the disease like spondyloarthritis despite the data for crystal induced arthropathy. According to our results hyperuricemia and MNU crystals in the context of primary psoriasis should be interpreted as a common complication of the disease. Therefore, we believe that the level of UA in blood and signs of secondary gout should always be searched in psoriatic patients. The differentiation between the two types of arthritis (psoriatic or crystal induced arthropathy) is necessary due to the different therapeutic approach – in some case biological therapy and at the other – urate-lowering drugs. From the 3 cases considered, it can be concluded that the timely established diagnosis and initiation of appropriate therapy can help to avoid the complications and increase the quality of life of the patients. We believe that using the ultrasound as a routine into the rheumatological daily practice will contribute to a more accurate and correct diagnosis and optimal therapeutic approach.

**Abbreviations:**

ACR – American College of Rheumatology
CRP – C-reactive protein
G – Gout
MCP – Metacarpophalangeal joints
MTP – Metatarsophalageal
PASE – Psoriatic arthritis screening and evaluation
PASI – Psoriasis Area and Severity Index
PIP – Proximal interphalangeal joints
PsA – Psoriatic arthritis
PV – Psoriasis vulgaris
RA – Rheumatoid arthritis
UA – Uric acid
WHO – World Health Organisation

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