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Mini Review

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Aquagenic Pruritus: First Manifestation of Polycythemia Vera

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ABSTRACT

Aquagenic Pruritus (AP) can be a first symptom of systemic disease; especially strong correlation with myeloproliferative disorders was described. In Polycythemia Vera (PV) patients its prevalence varies from 31% to 69%. In almost half of the cases AP precedes the diagnosis of PV and has significant influence on sufferers' quality of life. Due to the lack of the insight in pathogenesis of AP the treatment is still largely experiential. However, the new JAK1/2 inhibitors showed promising results in management of AP among PV patients.

KEYWORDS: Aquagenic pruritus; Polycythemia vera; JAK inhibitors.

Aquagenic pruritus (AP) is a skin condition characterized by the development of intense itching without observable skin lesions and evoked by contact with water at any temperature. Its prevalence varies from 31% to 69% in Polycythemia vera (PV) patients.[1,2,3] It has significant influence on sufferers' quality of life and can exert a psychological effect to the extent of abandoning bathing or developing phobia to bathing. Although, AP as an important clinical feature of PV was described for the first time more than 3 decades ago, its pathophysiology, frequency and management have not been fully established.[1,4]

PV-associated pruritus is characterized by patients as a generalized itching, tingling, burning or pricking skin sensation appearing mainly after contact with water, especially during warm bath or shower, but it could also be triggered by sudden change in temperature, sitting next to a fire-place or just sweating after exercises. AP tends to occur on extensor surfaces of the limbs, inter-scapular area, chest and abdominal wall with varying severity–from occasional, mild symptoms to severe, prolonged itching.[5]

PV is one of the most common myeloproliferative neoplasms characterized by indolent course and usually recognized incidentally by the discovery of high hemoglobin or hematocrit concentration. Whereas the onset of AP precedes diagnosis of PV in almost half of the cases,[5] a small number of patients presenting with AP provokes the physicians to consider a hematologic condition as an underlying cause. There is an easy opportunity for improvement in the process of establishing a final diagnosis among patients with AP, because a complete blood count conducted as a routine can be highly informative and may prevent the occurrence of fatal complications of PV, including venous or arterial thrombosis. Of note, AP may also occur simultaneously or just follow the diagnosis of PV.[6]

One of our patients–55-years old Caucasian male was admitted to our department with history of a non-resolving pruritus of 2-years duration, distributed on the lower limbs and trunk. Itch appeared mainly few minutes after bathing or showering in hot water and lasts for about one hour. Moreover, pruritus occurred sometimes spontaneously. The intensity of itching sensation after contact with water during the last three days before admission was assessed by patient as 5 points using Visual Analogue Scale (VAS) (range, 0 [no itching] to 10 [the worst itching imaginable]). The exacerbation of the symptoms occurred mainly in summer months. In medical history of the last months a fatigue and redness of cheeks were also reported. In the

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treatment of pruritus antihistamines (levocetirizine dihydrochloride), high potency corticosteroids (clobetasol propionate 0.05 % ointment) and emollients were used. Patient was investigated few times by general practitioner and dermatologist, nevertheless prescribed medications did not bring him any relief of itch. In conducted laboratory tests, high hemoglobin (25 g/dL), red blood cell ($6.3x10^6$ µL) and hematocrit (62%) levels were found; consequently the diagnosis of PV was suspected. Hematologic evaluation revealed JAK2V617F gene mutation and typical bone marrow changes confirmed the diagnosis of PV. Initially, the repeated phlebotomy and simultaneously given hydroxyurea of 500 mg daily dose were managed. The reduction of pruritus was achieved. After three months of hematologic treatment, the patient reassessed itching severity after contact with water as 3 points in VAS scale. The sustenance of improvement remains unknown.

Differential diagnosis of AP should rule out presence of other subtypes of AP, including idiopathic or AP of the elderly. One third of patients with idiopathic AP have family history of AP with tendency toward AP appears to be hereditary, whereas in AP of the elderly itching sensation affects mostly female patients above 60-years old with clinical features of dry skin.[7] It has also been linked to several conditions such as juvenile xanthogranuloma,[8] myelodysplastic syndrome,[9] T-cell non-Hodgkin's lymphoma,[10] hepatitis C infection,[11] drugs like bupropion[12] or hormonal replacement therapy[13] and idiopathic hypereosinophilic syndrome.[14]

The pathophysiology of PV-associated pruritus remains still poorly understood. Early studies have shown increased acetylcholinesterase activity in the nerve fibers surrounding eccrine sweat glands[15] and higher histamine levels.[16] However, others did not confirm these correlations.[3] Previous reports have revealed significantly elevated number of cutaneous mononuclear cells and eosinophils after water challenge, and manifestation of mast cell degranulation.[17] Moreover, Tefferiet al[18] proved that patients demonstrating homozygosity for the JAK2V617F mutation had a significantly higher incidence of pruritus (69% *vs.* 38%, p=0.04) in comparison with heterozygous patients, while Siegel et al[5] and Pieri et al[19] revealed the presence of the JAK2 mutation in the mast cells and basophils of the skin of patients with PV, respectively.

Management of PV-associated AP is unceasingly challenging. The lack of insight in the mechanism of cutaneous induction of AP is partly responsible for the inadequacy of current symptomatic treatment. Similarly to described case, patients often are taking various medications; generally with modest success. Improvement or even resolution of pruritus may be achieved after correction of hematological parameters of PV in some of the patients, while in others there may be no noticeable difference.[7] The most effective drug in control of AP used in PV sufferers is Interferon alfa (IFN-α). Previous data consisting of 16 prospective studies and three case reports involving 279 patients established that IFN-α reduced significantly itching sensation in 81% patients.[20] Other "popular" hematological options include busulphan, hydroxyurea and danazol, which were able to improve pruritus in 88%, 45% and 75%, respectively.[7] Of note, the populations of above mentioned groups were small–four patients in each. Phlebotomy is another frequently therapy used, but it shows mixed results with predominance of poor outcome in terms of PV-associated pruritus. Photochemotherapy (PUVA) was evaluated as good treatment modality and has been found superior to UVB-phototherapy in the terms of controlling of PV-associated pruritus.[21] The analysis of the efficacy of Selective Serotonin Reuptake Inhibitors (SSRI) in the group of 10 patients with AP confirmed that 80% of them had a near total or total resolution of pruritic sensations.[22] Antihistamines demonstrate mixed efficacy results and should not be so readily recommended.[7] Promising early results in the treatment of AP in population of PV sufferers were found with new JAK1/2 inhibitors. In the studies on ruxolitinib–JAK2/JAK1-inhibitor, the Response Rates (RR) for AP were up to 92%[23] and the selective JAK2 inhibitor (TG101348) trial showed a clinically significant reduction in pruritus with RR of 75% (50% with complete resolution).[24] Administration of an inhibitor of the mammalian target of rapamycin (mTOR) to patients with post-PV or essential thrombocytopenia myelofibrosis resulted in complete resolution of AP in all the five patients affected.[25]

In conclusion, pruritus associated with PV remains still underestimated clinical feature, despite AP is a common symptom resulting in significant morbidity. Pathogenesis of PV-related pruritus remains to be elucidated, although recent data about ongoing clinical trials with JAK2/JAK1 and mTOR inhibitors present favorable prospect with regard to the mechanisms and effective treatment strategies for aquagenic pruritus in polycythemia vera.

CONFLICTS OF INTEREST: None.

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