Infections in Hospitalized Patients with Psoriasis in a Skin Referral Hospital

Nafise Zaredar[1], Hamidreza Mahmoudi[1,2], Tahereh Soori[1,3], Amir Teimourpour[1], Kamran Balighi[1,2], Ali Salehi Farid[1,2], Maryam Daneshpazhooh[1,2]

1 Department of Dermatology, Tehran University of Medical Sciences, Tehran, Iran
2 Autoimmune Bullous Diseases Research Center, Tehran University of Medical Sciences, Tehran, Iran
3 Department of Infectious Diseases, Tehran University of Medical Sciences, Tehran, Iran

Corresponding Author: Maryam Daneshpazhooh, Razi Hospital, Vahdate-Eslami Sq, Tehran 11996 Iran; ORCID 0000-0003-1020-8895 Phone number and fax: +98-21-55618989; Email: maryamdanesh.pj@gmail.com

ABSTRACT

Introduction: Psoriasis and its treatments may predispose patients to various infections. This is considered one of the most significant complications in patients with psoriasis.

Objectives: In the present study, we aimed to determine the prevalence of infection in hospitalized psoriasis patients and its relationship with systemic and biologic treatments.

Methods: All hospitalized patients with psoriasis from 2018 to 2020 in Razi Hospital in Tehran, Iran, were studied and cases of infection were recorded.

Results: Overall, 516 patients were studied and 25 types of infection in 111 patients were found. The most common types of infection were pharyngitis and cellulitis, followed by oral candida, urinary tract infections, common cold, fever of unknown origin, and pneumonia. Female sex and pustular psoriasis were significantly associated with infection in psoriatic patients. Those patients who received prednisolone had a higher risk of infection, and those under treatment with methotrexate or infliximab had a lower risk of infection.

Conclusion: Overall, 21.5% of psoriasis patients in our study had at least one episode of infection. This demonstrates that the prevalence of infection in these patients is not low. Using systemic steroids was associated with a higher risk of infection, while using methotrexate or infliximab was concomitant with a lower risk of infection.

Introduction

Psoriasis is a common, chronic, inflammatory cutaneous disease, causing morbidity and mortality in severe cases. The approximate prevalence rate is 0.14-5.32% of the general population. [1, 2]

The characteristic of psoriasis is sustained inflammation which causes uncontrolled proliferation of keratinocytes and dysfunctional differentiation that activates through TNF-α, IL-17, and IFN-γ.

The psoriatic plaque's histology shows acanthosis, which covers inflammatory infiltrates consisting of dermal dendritic cells, macrophages, T cells, and neutrophils as well as neovascularization [3].

Infections are among the most concerning complications of psoriasis per se and its treatments. Two types of conventional and biological treatments are used to treat this disease. Biologic treatments are mostly used in more severe psoriasis patients; however, infections are the most crucial side effect of these drugs. Recent studies have found conflicting results regarding the prevalence of infection in this disease and its relationship with various systemic treatments. This study evaluated the prevalence of infection in psoriasis hospitalized patients in a skin referral hospital and its relationship with variables such as biologic treatments in hospitalized patients with psoriasis.

Methods

In this retrospective cross-sectional study, all hospitalized psoriasis patients from 2018 to 2020 in Razi Hospital in Tehran, Iran were examined for any documented infection. Demographic data, psoriasis subtypes, the existence of arthropathy, and present treatments (methotrexate, prednisolone, cyclosporine, acitretin, phototherapy, topical treatment, and biological treatment) were extracted. Furthermore, the wound, blood, and urine culture results were recorded. All hospital records over the course of the study were reviewed and cases of diagnosed psoriasis were included in the study. Cases of comorbid psoriasis with other skin disease were excluded.

These data were analyzed with SPSS software (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp). Associations between infections and other variables were examined using the Chi-Square test. The frequency has been calculated for quantitative data, mean and standard deviation, for qualitative data. The significance level was considered a P-value < 0.05. Confidence interval (CI) is the range of values between which you expect your estimate to be if you repeat your test, at a certain level of confidence.

An odds ratio (OR) is a measure of how an exposure relates to a result. The OR represents the probability that a result will occur as a result of a particular exposure compared to the probability that the result will occur in the absence of that exposure.

Results

Among 516 patients, 172 (33%) women and 344 (67%) men, with a mean age of 43.85 +/- 15.95 (range: 8 to 89). The mean age of men was greater than women (44.97 +/- 15.40 vs 41.62 +/- 16.83) (P- value: 0.024).

380 (73.6%), 106 (20.5%), 25 (4.8%), 4 (0.8%) and 1(0.2%) were plaque-type, pustular, erythrodermic, inverse and guttate, respectively.

Furthermore, from 248 available data, 144 (58.06%) patients had arthropathy. Meanwhile, 111 (21.5%) patients had at least one episode of infection; overall, 166 cases were detected.

Considering the low number of patients with inverse and guttate psoriasis, only plaque-type, pustular and erythrodermic psoriasis were analyzed.

The most common types of infection were pharyngitis, cellulitis followed by oral candidiasis, urinary tract infections (UTI), common cold, fever of unknown origin (FUO), and pneumonia (Table 1).

There was a significant correlation between age and oral candidiasis, UTI, and herpes simplex virus (HSV) infection (P-values: 0.023, 0.012, 0.001, respectively), while no significant relationship was found between age and other types of infections (P-value<0.05 for all).

Infections were 2 times more frequent in women (30.2%) than men (17.2%) (OR: 2.09, 95%CI: 1.36-3.21, P-value: 0.001). Additionally, oral candidiasis, flexural candidiasis, and erythrasma were significantly more common in women (P-values: 0.011, 0.044, 0.001, respectively).

Regarding psoriasis subtypes, there was a significant relation between plaque-type and pustular psoriasis with infection (P-values: <0.001, OR: 0.282; P-value <0.001, OR: 3.845, respectively). In other words, patients with pustular and plaque-type psoriasis had a 3.8 and 2.8 times higher risk of infection in comparison with other subtypes, respectively. Furthermore, cellulitis, pharyngitis, FUO, oral candidiasis, UTI, vaginal candidiasis, and bacterial blepharitis were significantly more common in the pustular subtype (Table 2).

Concerning the relationship between medications and infection, patients treated with prednisolone (OR: 2.93, 95%CI: 1.82-4.73, P-value< 0.001) had a higher risk of infection. From a total of 99 cases on prednisolone, 38 (38.4%) had at least one episode of infection, while the infection was seen in 73 (17.5%) out of 417 cases who were not receiving prednisolone (P-value: <0.001, OR: 2.93). On the other hand, those under treatment of methotrexate (OR: 2.1, 95%CI: 0.29-0.76, P-value: 0.002) or infliximab (OR: 5.12, 95%CI: 0.10-0.35, P-value< 0.001) had a lower risk of infection (Table 3).

Table 1. Types of infections and frequency of each occurrence in psoriatic patients.

| Type of infection | Number of infections | | | Total/Person | Total/Infection |
	1	2	3		
Cellulitis	20	1	-	21	22 (13.25%)
Pharyngitis	26	-	1	27	29 (17.47%)
Common cold	11	-	-	11	11 (6.62%)
Pneumonia	7	-	-	7	7 (4.21%)
Paronychia	3	-	-	3	3 (1.8%)
FUO	5	-	1	6	8 (4.82%)
Oral Candida	17	1	-	18	19 (11.44%)
Conjunctivitis	5	1	-	6	7 (4.21%)
UTI	12	1	1	14	17 (10.24%)
HBV	3	-	-	3	3 (1.8%)
HCV	4	-	-	4	4 (2.41%)
HIV	3	-	-	3	3 (1.8%)
HSV	3	-	-	3	3 (1.8%)
Erythrasma	6	-	-	6	6 (3.61%)
Gastroenteritis	4	-	-	4	4 (2.41%)
Otitis externa	2	-	-	2	2 (1.2%)
Tuberculosis	1	-	-	1	1 (0.6%)
Epididymitis	1	-	-	1	1 (0.6%)
Axillary abscess	1	-	-	1	1 (0.6%)
Septic arthritis	2	-	-	2	2 (1.2%)
Impetigo	1	-	-	1	1 (0.6%)
Flexural candidiasis	7	-	-	7	7 (4.21%)
Folliculitis	1	-	-	1	1 (0.6%)
Vaginal Candidiasis	2	-	-	2	2 (1.2%)
Blepharitis	2	-	-	2	2 (1.2%)
Total					166

FUO: fever of unknown origin, UTI: urinary tract infection, HBV: hepatitis B virus, HCV: hepatitis C virus, HIV: human immunodeficiency virus, HSV: herpes simplex virus

Table 2. The relationship between psoriasis subtypes and the most prevalent infection types.

	Plaque type	Non-plaque type	P-value	Pustular type	Non-pustular type	P-value
Cellulitis	8 (2.1%)	13 (9.6%)	0.000	11 (10.4%)	10 (2.4%)	0.001
Pharyngitis	15 (3.9%)	12 (8.8%)	0.028	11 (10.4%)	16 (3.9%)	0.008
FUO	1 (0.3%)	5 (3.7%)	0.006	4 (3.8%)	2 (0.5%)	0.018
Oral Candidiasis	7 (1.8%)	11 (8.1%)	0.002	9 (8.5%)	9 (2.2%)	0.004
UTI	7 (1.8%)	7 (5.1%)	0.061	6 (5.7%)	8 (2%)	0.047
HSV	0 (0%)	3 (2.2%)	0.018	2 (1.9%)	1 (0.2%)	0.109
Vaginal Candidiasis	0 (0%)	2 (1.5%)	0.069	2 (1.9%)	0 (0%)	0.042
Blepharitis	0 (0%)	2 (1.5%)	0.069	2 (1.9%)	0 (0%)	0.042

In patients on prednisolone, the risk of cellulitis, pharyngitis, common cold, FUO, UTI, and blepharitis was higher. Additionally, cyclosporine was associated with a higher risk of FUO and patients receiving methotrexate had a lower chance of pharyngitis (Table 4).

Regarding the anti-TNFα group, infliximab was associated with a lower risk of cellulitis (OR:0.04, P-value: 0.001) (Table 4), while adalimumab and etanercept were not linked to any type of infection (all p-values>0.05). It is worth noting that although no case of active tuberculosis was recognized,

Table 3. The relationship between infections and current treatments.

| | | | Infection | | | | | |
			No	Yes	Total	P-value	OR	95%CI
Methotrexate	No	Count	237	83	320	**0.002**	0.47	0.29-0.76
		%	74.10%	25.90%	100.00%			
	Yes	Count	168	28	196			
		%	85.70%	14.30%	100.00%			
Prednisolone	No	Count	344	73	417	**0.000**	2.93	1.82-4.73
		%	82.50%	17.50%	100.00%			
	Yes	Count	61	38	99			
		%	61.60%	38.40%	100.00%			
Cyclosporine	No	Count	386	103	489	0.29	1.57	0.67-3.7
		%	78.90%	21.10%	100.00%			
	Yes	Count	19	8	27			
		%	70.40%	29.60%	100.00%			
Acitretin	No	Count	249	54	303	0.075	1.68	0.81-1.57
		%	82.20%	17.80%	100.00%			
	Yes	Count	186	27	213			
		%	87.32%	12.68%	100.00%			
Phototherapy	No	Count	375	100	475	0.38	1.37	0.66-2.84
		%	78.90%	21.10%	100.00%			
	Yes	Count	30	11	41			
		%	73.20%	26.80%	100.00%			
Topical	No	Count	92	22	114	0.51	1.18	0.7-2
		%	80.70%	19.30%	100.00%			
	Yes	Count	313	89	402			
		%	77.90%	22.10%	100.00%			
Infliximab	No	Count	241	98	339	**0.000**	0.19	0.10-0.35
		%	71.10%	28.90%	100.00%			
	Yes	Count	164	13	177			
		%	92.70%	7.30%	100.00%			
Adalimumab	No	Count	401	110	511	1	0.91	0.1-8.23
		%	78.50%	21.50%	100.00%			
	Yes	Count	4	1	5			
		%	80.00%	20.00%	100.00%			
Etanercept	No	Count	401	110	511	1	0.91	0.1-8.23
		%	78.50%	21.50%	100.00%			
	Yes	Count	4	1	5			
		%	80.00%	20.00%	100.00%			
Total		Count	405	111	516			
		%	78.50%	21.50%	100.00%			

63 (12.2%) patients received isoniazid due to positive PPD and use of immunosuppressive therapy.

Culture results were available in 82 cases; 45 (54.8%) were negative. Staphylococcus epidermidis (36.36%) followed by Enterobacter (9.09%) were the most commonly detected micro-organisms in blood cultures. In urine cultures, E-coli (18.51%) followed by Pseudomonas (11.11%), and in wound cultures, Staph epidermidis (29.76%) followed by Staphylococcus aureus (28.57%) were the most common pathogens.

Table 4. The relationship between treatments and the most prevalent infection types.

	Methotrexate		Prednisolone		Cyclosporine		Infliximab	
	P-value	OR	P-value	OR	P-value	OR	P-value	OR
Cellulitis	0.172	0.497	**0.042**	2.73	0.302	1.97	**0.001***	0.04
Pharyngitis	**0.032***	0.355	**0.016**	2.64	0.645	1.48	0.346	0.65
Common cold	0.755	1.37	**0.009**	5.31	1	0.75	0.108	0.18
FUO	0.088	0.12	**0.001**	22.12	**0.035**	9.7	0.669	0.38
UTI	0.703	1.23	**0.034**	3.29	0.533	1.408	0.154	0.31
Blepharitis	0.528	0.32	**0.037**	21.41	0.102	18.77	1	1.92

*Negative correlation

Discussion

In the present study, we found that 21.5% of hospitalized psoriasis patients had at least one episode of infection; a total of 25 types were recorded in 111 patients. Men outnumbered women in this study, which may reflect more severe disease needing hospitalization in men. However, psoriatic women were more prone to infections.

In our study, the most common types of infection were pharyngitis (n=29), cellulitis (n=22), oral candidiasis (n=19), UTI (n=17), common cold (n=11), FUO (n=8) and pneumonia (n=7).

There was a significant correlation between age and oral candidiasis, UTI, and HSV. Previous studies have shown a higher prevalence of oral and cutaneous candida colonization and infection in psoriasis. [4, 5] Similarly, in the present study, oral candidiasis was the third most common infection, especially seen in the elderly; this may be partly attributed to dentures. Meanwhile, the older age of prevalence of UTI could be due to more common genitourinary problems in the elderly and lack of personal hygiene in this group.

We did not have precise details regarding the reason for the patients' hospitalization, although it was primarily due to the psoriasis flare-up and not the infections per se. The most serious infections that led to hospitalization in this study were probably cellulitis followed by UTI.

In a Prospective Cohort Study from the British Association of Dermatologists Biologic and Immunomodulators Register, the most common types of infection in psoriatic patients were lower respiratory tract infections, followed by skin and soft tissue infections, and urinary tract infections. [6] While in a cohort study in the United Kingdom, upper and lower respiratory tract infections were the most prevalent. [7] In addition, a population-based cohort in the Netherlands showed that respiratory tract, abdominal, and skin infections occurred most frequently in patients with psoriasis. [8] Another study in a multicenter, longitudinal, disease-based registry (PSOLAR) reported that the most common types of serious infections were pneumonia and cellulitis. [9] Likewise, in the present study, the most common infections were respiratory tract infections followed by skin infections and UTIs.

In terms of the psoriasis subtypes, 50% of inverse, 42.5% of pustular, 24% of erythrodermic, and 15.3% of plaque-type psoriasis had a history of infection. In the present study, the chance of infection in patients with pustular psoriasis was 3.8 times higher than with other types; however, because of the low frequency of inverse psoriasis, the high frequency of infections in this group cannot be inferred.

Patients with psoriasis may be more susceptible to infections due to both the disease per se and the immunosuppressive medications. Previous studies have shown conflicting results about the correlation between different treatments and the risk of infection. The essential difference between the biologic and conventional treatments, using combination therapies, could be considered possible reasons for this discrepancy.

In our study, cyclosporine was significantly associated with FUO, although the overall risk of infection was not higher in contrast to Sejio et al., who reported a higher risk of overall and serious infections. [10] Likewise, prednisolone was associated with 2.93 times more frequent infections. Furthermore, we did not find any relationship between acitretin and infections, while Seijo et al. reported a lower risk of infection with acitretin. [10] These controversial results could be due to the predominant use of acitretin as a combination therapy with other drugs in the present study. Another controversial finding of our study was the lower risk of infection among patients treated with methotrexate, which is not in concordance with its immunosuppressive nature.

These controversies also exist in the prevalence of infections in psoriasis patients using biologic drugs. Hsu et al. stated that biologic treatments might increase the risk of

infection by controlling the inflammatory process and decreasing the disease severity or increasing this risk by suppressing the immune system. [11] In the present study, patients being treated with TNF-a inhibitors did not have any increase in infection risk, and even a lower risk of cellulitis was detected among patients using infliximab. Carneiro et al. [12] and Wakkee et al. [8] did not report any increase in infection risk in patients using biologic treatments compared with conventional drugs. Likewise, according to the Yiu et al. [13] and Garcia-Doval [14] studies, no increased risk of serious infections was found in patients on anti-TNF treatments. On the other hand, Yiu et al. have shown that infliximab was associated with a two-fold increased risk of serious infections compared with non-biologic treatments and a 3-fold increased risk compared with methotrexate. [15] Additionally, in a cohort study, Kalb et al. showed that serious infections were more likely to occur with adalimumab and infliximab than with non-biologic and non-methotrexate treatments. [9] Likewise, in three other studies, the authors found a higher risk of infection in biologic treatment compared with conventional treatments.

In recent studies, Systemic-immune inflammation index (SII) (neutrophil X platelet/lymphocyte) as a new complete blood cell index has been used in the prediction of disease progression and was associated with psoriasis activation and severity. Significantly higher SII values were present in higher PASI scores and indicated increased inflammatory response and poor prognosis. SII can also be an additional indicator of disease activation in autoimmune diseases such as Behçet's disease. [16, 17]

Limitation

This retrospective survey was restricted solely to inpatient psoriatic cases admitted in the dermatology ward of a skin referral hospital. Therefore, information about patients treated in outpatient clinics and those hospitalized in general hospitals was unavailable. This study was conducted before the COVID-19 outbreak; therefore, it lacks data regarding the relationship between the risk of COVID-19 infection and the variables mentioned above.

Conclusion

Overall, 21.5% of psoriasis patients in the present study had at least one episode of infection. We observed an increased risk of infection in patients receiving prednisolone, while there was no increase in infection risk in patients treated with biologic drugs and even a relatively reduced risk in MTX-treated patients.

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