Skin Manifestations in Patients with Adult-onset Immunodeficiency due to Anti-interferon-gamma Autoantibody: A Relationship with Systemic Infections

Kamonwan JUTIVORAKOOL¹, Prattana SITTIWATTANAWONG², Kornphaka KANTIKOSUM², Cameron P. HURST¹, Chanat KUMTORNURT², Pravit ASAWANONGA, Jetanong KLAESONGKRAM³ and Pawinee RERKNIMITR²

¹Division of Infectious Diseases and ²Dermatology Unit, Department of Medicine, King Chulalongkorn Memorial Hospital, Thai Red Cross Society, ¹Division of Dermatology, Department of Medicine, Center for Excellence in Biostatistics and ¹Division of Allergy and Clinical Immunology, Department of Medicine, Faculty of Medicine, Skin and Allergy Research Unit, Chulalongkorn University, Bangkok, Thailand

Abstract

Adult-onset immunodeficiency due to anti-interferon-γ autoantibody is an emerging acquired immunodeficiency with frequent skin manifestations. A retrospective chart review was conducted and identified 41 patients with the syndrome. Skin involvement was detected in 33 (80%) patients, 15 (45%) with infective skin diseases and 27 (65%) with reactive skin disorders. Reactive lesions were mostly neutrophilic dermatoses, e.g. Sweet syndrome. Of note, the presence of neutrophilic dermatoses was highly associated with infections of other sites. An adjusted odds ratio for the existence of infections in patients with neutrophilic dermatoses was 14.79 (95% CI: 5.13, 42.70; p < 0.001). Moreover, neutrophilic dermatoses were significantly correlated with opportunistic infections observed in those with defects in cell-mediated immunity including non-tuberculous mycobacterium and disseminated fungal infection. The odds ratio for opportunistic infections in the presence of neutrophilic dermatoses was 12.35 (95% CI: 5.00, 30.55; p < 0.001). Thus, the presence of neutrophilic dermatoses in patients with the syndrome can signal opportunistic infections that warrant physicians’ attention.

Key words: skin signs; neutrophilic dermatoses; Sweet syndrome; IFN-gamma; autoantibody; acquired immunodeficiency.

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Corr: Pawinee Rerknimitr, MD, MsC, Division of Dermatology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, 1873 Rama IV Road, Pathumwan, Bangkok 10330, Thailand. E-mail: pawinee.r@chula.ac.th

Adult-onset immunodeficiency due to anti-interferon-γ autoantibody is an emerging acquired immunodeficiency, also known as AIDS-like illness in non-HIV-infected individuals. Skin manifestations, mostly neutrophilic dermatoses (ND) e.g. generalized pustular eruption is a frequent feature. Of note, the presence of ND was highly associated with the existence of infections of other sites. The presence of ND in patients with the syndrome can signal opportunistic infections that warrant physicians’ attention.

Significance

An adult-onset immunodeficiency due to anti-interferon-γ autoantibody is an emerging acquired immunodeficiency, also known as AIDS-like illness in non-HIV-infected individuals. Skin manifestations, mostly neutrophilic dermatoses (ND) e.g. generalized pustular eruption is a frequent feature. Of note, the presence of ND was highly associated with the existence of infections of other sites. The presence of ND in patients with the syndrome can signal opportunistic infections that warrant physicians’ attention.

Materials and Methods

Study design and ethical consideration

A retrospective chart review was conducted in King Chulalongkorn Memorial Hospital, Bangkok, Thailand. A patient registry with adult-onset immunodeficiency due to anti-IFN-γ autoantibody was established in our hospital since 2000. From this 16-year period (2000–2015), we were able to identify 41 patients in our registry. Detailed information of every patient visit was retrieved and subsequently analyzed. The study protocol was approved by the local Institutional Review Board (no 245/59).
Study population and definitions

Adult-onset immunodeficiency due to anti-IFN-γ autoantibody was diagnosed when patients met all the following criteria: Aged between 18 to 80 years old, anti-IFN-γ autoantibody detected in the serum by enzyme-linked immunosorbent assay (ELISA), negative test for anti-HIV antibody, presence of at least two episodes of culture, PCR or histopathology-proven infections caused by uncommon intracellular organisms including NTM, disseminated fungal infections (e.g., infection due to Talaromyces marneffei, cryptococcosis, histoplasmosis), non-typhoidal Salmonella bacteria, and disseminated herpes zoster infection. Patients were excluded from the study if they had history or active malignancy or received immunosuppressive therapy, i.e. systemic corticosteroids within 4 weeks of opportunistic infection diagnosis.

The detection of anti-IFN-γ autoantibody was done using ELISA technique. The protocol was modified from those that have been reported (6, 8). Briefly, microtiter plates were coated with 100 µl IFNγ (2 µg/ml) (R&D Systems) per well and incubated at 4°C overnight. The plates were washed 3 times with 200 µl PBST (0.1% Tween-20, Sigma). Patient’s diluted plasma (1:100), 100 µl/well was added to each well and then incubated at room temperature for 2 h. After washing 3 times with PBST, wells were incubated with 100 µl 1:2,000 sheep anti-human IgG-HRP (GE Healthcare Bio-Sciences) for 1 h. After washing, 100 µl TMB solution (2N H2SO4) was added. The reading of the optical density (OD) was made at 450–550 nm. A positive test was determined when the OD was more than 2 which was approximately 2-fold (OD) was made at 450–550 nm. A positive test was determined when the OD was more than 2 which was approximately 2-fold the value of the normal controls (6).

ND comprise skin conditions with polymorphonuclear leukocyte infiltration into different levels of the skin (9, 10). We carefully reviewed that skin lesions in cases diagnosed under ND were proven sterile by appropriate staining techniques, cultures or PCR studies. Sweet syndrome was verified using well-established criteria (11). In addition, diagnosis of leukocytoclastic vasculitis (LCV) and panniculitis were confirmed by histopathology. Infections of other sites are defined as systemic infections/involvement in our study.

Statistical analysis

Patient characteristics at baseline were described using counts and percentages for categorical variables and means and standard deviations for continuous measures. As the outcome variable in this study was binary, and measured repeatedly over time, we employed a binary logistic mixed effect regression to generate odds ratios (OR). All analyses were conducted using the R Statistical Package (v3.4.1; R Core Team, 2017) (12) and mixed effect modeling was conducted using the R library lme4 (13). A significance level of 0.05 was used throughout all inferential analyses.

RESULTS

From 2000 to 2015, we identified 41 patients who met the criteria for diagnosis. The study included a total of 300 outpatient visits with a mean ± standard deviation (SD) follow-up period of 42.66 ± 41.51 months. The longest follow-up time was 180 months. Patient mean age was 54 years old and ranged from 25–78 years. A slight male preponderance was observed (number of male vs female patients, 25 (61%) and 16 (39%), respectively) and over two-thirds (68%) of the patients did not have underlying diseases. Baseline characteristics and demographic data are shown in Table SI1.

The most common organ involvement was the skin followed by the lymph nodes and blood stream (number of patients (%), 33(80%), 29(71%) and 23(56%), respectively). Three (7%) patients died with causes of death being disseminated histoplasmosis, septicemia due to group A streptococcus, and myocardial infarction.

Skin manifestations were found in 33 (80%) patients. Of these, 27 (82%) patients were observed with reactive skin conditions, whereas 15 (45%) patients had infective skin diseases. It should be noted that 9 (27%) patients suffered from both reactive and infective skin abnormalities. Table I provides the types and number of patients with skin involvement.

Reactive skin diseases detected in patients were mainly ND (Table II). Numerous sterile non-follicular pustules on erythematous and edematous skin were found in 7 patients. In two, lesions were mainly confined to the face and in the flexural folds whereas the other 5 patients had more widespread eruption (Fig. 1). None of these patients with generalized pustular eruption had a history of new drug usage. Patients with Sweet syndrome (n = 9) exhibited erythematous plaques and nodules that were mostly found in more than one region of the body. Lobu-
lar panniculitis was also observed \( n = 1 \). No ulceration was found in the panniculitis patient.

Histopathology of these ND showed neutrophilic infiltration into different levels of the skin. For generalized pustular eruptions, subcorneal and/or intraepidermal pustules were observed. A direct immunofluorescence study was not performed in these patients. In Sweet syndrome patients, histology revealed a dense neutrophilic infiltration in the dermis (Fig. 1). Histopathology of lobular panniculitis showed aggregation of inflammatory cells predominantly composed of neutrophils in the adipocyte lobules. A comparison of laboratory data between patients with and without reactive skin diseases showed significantly higher numbers of white blood cell, absolute

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**Table II. Neutrophilic dermatoses (ND) in patients with adult-onset immunodeficiency due to anti-interferon-γ autoantibody**

<table>
<thead>
<tr>
<th>Types</th>
<th>No. of episodes</th>
<th>Clinical features</th>
<th>Treatment</th>
<th>Response Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized pustular eruption</td>
<td>8</td>
<td>Generalized pustular eruptions on the forearm, trunk and legs</td>
<td>Dexamethasone 10 mg iv/day, ( n = 1 )</td>
<td>Improved in 4 ± 3.16 weeks</td>
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<td></td>
<td></td>
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<td>MTX 15 sc weekly, ( n = 1 )</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Topical corticosteroids, ( n = 4 )</td>
<td></td>
</tr>
<tr>
<td>Lobular panniculitis</td>
<td>1</td>
<td>Nodules on the forearms and legs</td>
<td>No specific treatment, ( n = 1 )</td>
<td>Spontaneous resolved</td>
</tr>
<tr>
<td>Sweet syndrome</td>
<td>9</td>
<td>Erythematous edematous plaques and papules; localized in 3 and generalized ( ^2 ) in 5 episodes. The locations of the lesions are the forearms, face, legs and the trunk (4, 2, 1 and 5 episodes), respectively</td>
<td>Prednisolone 0.5–1 mg/kg/day, ( n = 3 )</td>
<td>Improved in 4.17 ± 2.62 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Prednisolone 0.5 mg/kg/day + colchicine 0.6 mg od-bid, ( n = 2 )</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Prednisolone 1 mg/kg/day + colchicine 0.6 mg bid + dapsone 100 mg OD, ( n = 1 )</td>
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<td></td>
<td></td>
<td></td>
<td>Topical corticosteroids, ( n = 1 )</td>
<td></td>
</tr>
<tr>
<td>Neutrophilic reactions NOS*</td>
<td>9</td>
<td>Erythematous papules, nodules and/or pustules; localized in 1 and generalized ( ^2 ) in 5 episodes. Locations of the lesions are the forearms, face, legs and the trunk (3, 1, 3 and 4 episodes), respectively</td>
<td>Topical treatment and colchicine 0.6 mg bid, ( n = 3 )</td>
<td>Improved in 8.29 ± 7.61 weeks</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Topical treatment and prednisolone 20 mg/day, ( n = 1 )</td>
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<td></td>
<td></td>
<td></td>
<td>Topical treatment alone, ( n = 2 )</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>No treatment, ( n = 1 )</td>
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</tbody>
</table>

*a some patients experienced multiple episodes of ND; b lesions presented in more than one body region; *Neutrophilic reactions NOS: the condition was diagnosed when erythematous papules, nodules or pustules were detected, and histopathology revealed neutrophilic infiltrations in whom the criteria for diagnosis of Sweet syndrome were not met; sc: subcutaneous injection.

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**Fig. 1. Clinical features and histopathology of the skin manifestations**

(a, b, c) Clinical photographs of generalized pustular eruption (GPE) showing numerous sterile non-follicular pustules on the trunk, legs and forearms of the same patient; (d) Skin biopsy from the GPE patient showing subcorneal and intraepidermal collections of neutrophils (e, f) Patient with Sweet syndrome (SS), erythematous papules and plaques on the neck and shoulder; (g) Histology of the SS patient revealed a dense neutrophilic infiltration in the dermis; (h, i, j) Representative patient who exhibited both neutrophilic dermatosis (ND) and infections of other sites; (h) ND, multiple discrete erythematous papules and sterile pustules were found on the chest wall; (i) Enlargement of multiple cervical lymph nodes due to Mycobacterium abscessus infection; (j) Postinflammatory hyperpigmentation resulting from disseminated herpes zoster infection of C5–7–8, T1 dermatome; (d, g) Hematoxylin and eosin stain, original magnification × 40.

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neutrophil and eosinophil counts (all p<0.05) in patients with reactive skin diseases than those without (Table SII). Treatment of ND encompassed topical corticosteroids, dapsone, colchicine and systemic corticosteroids. Most patients responded well to therapy (Table II).

Other reactive skin lesions which were not ND were also observed e.g. leucocytoclastic vasculitis, erythema nodosum and papulovesicular eruption (Table I). Outstanding, we found a case of diffuse plane xanthoma, manifested as multiple well-defined flat-top yellow-orange plaques on medial eyelids, anterior neck and mid upper chest area with telangiectasia. The patient was a 58-year-old male with chronic recurrent *Mycobacterium szulgai* lymphadenitis and chronic viral hepatitis B infection. The lesions developed 6 years after diagnosis of the immunodeficiency syndrome. His serum protein electrophoresis and immunofixation studies revealed polyclonal gammapathy. Details of non-ND clinical presentations are summarized in Table SIII.

ND are often associated with systemic diseases. This prompted us to examine the association of ND with infections of other sites. Some patients suffered from ND more than once. There were 27 episodes of ND occurring in the cohort. Of these, 16 (59%) presented with concurrent infections. Sweet syndrome and generalized pustular eruption were the two most common ND found with the infections. Seven out of a total of 9 episodes (78%) of Sweet syndrome and 6 out of 8 events (75%) of generalized pustular eruption coincided with the infections. The co-infections were mainly NTM of the lymph nodes and blood stream. Details of type of ND, sites and species of infections are shown in Table SIV.

We further analyzed the OR for the occurrence of other site infections if ND were present. The OR was 12.33 relative to those without ND, and after adjusting for possible confounders including time, sex, age and the presence of underlying diseases, the adjusted OR was 14.79 (95% CI: 5.13, 42.70; p<0.001) (Table III) suggesting those with ND had a considerably higher risk of the existence of infections. We then further divided the infections into opportunistic infections (OI) which implied infections usually observed in patients with cell-mediated immunity (CMI) defects. These included NTM, histoplasmosis, cryptococcosis and an infection due to *Talaromyces marneffei*. The other group was composed of infections that can be found in immunocompetent individuals (non-OI) namely, salmonellosis, group A streptococcosis, melioidosis, and tuberculosis. The OR of OI in the presence of ND was 12.35 (95% CI: 5.00, 30.55; p<0.001) whereas the OR for non-OI was considerably lower (OR 1.52; 95% CI: 0.47, 4.91). The results indicated that ND were more substantially associated with OI. Details are shown in Table III.

Regarding the temporal relationship of reactive skin lesions with systemic infections, we found that reactive skin lesions predominantly occurred concurrently with systemic infections (median time to the occurrence of infections is 0, interquartile range (IQR) was 0, 18 weeks). Finally, patients with reactive skin lesions experienced more weight loss compared to those without. The percentage changes of body weight from baseline is significantly lower in patients with reactive skin lesions (mean of 2.1 ± 10.39 vs. −3.33 ± 6.45, p = 0.023, for those without and with reactive skin lesions, respectively).

### DISCUSSION

From the present study, we confirm that a significant proportion (80%) of patients with adult-onset immunodeficiency due to anti-IFN-γ autoantibody demonstrates skin involvement. These can be divided into reactive and infective skin lesions. In the reactive group, ND is predominant. Essentially, the presence of ND is significantly associated with the existence of infections of other sites with an adjusted OR of 14.79. Thus, when dermatologists encounter patients affected with the syndrome who present with ND, one should specifically search for opportunistic infections that may be occult at that state.

<table>
<thead>
<tr>
<th>Table III. Unadjusted and adjusted odd ratios (OR) of various factors in relation to the occurrence of infections in patients</th>
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<tbody>
<tr>
<td><strong>Effects</strong></td>
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<tr>
<td>Presence of reactive skin lesions</td>
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<tr>
<td>Neutrophilic dermatoses</td>
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<tr>
<td>Non-neutrophilic dermatoses</td>
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<tr>
<td>Time</td>
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<td>Sex</td>
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<tr>
<td>Presence of underlying diseases</td>
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<td>Age, 10</td>
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<tr>
<td>Region</td>
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<td>Northeastern</td>
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<td>Central</td>
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<td>East</td>
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<td>South</td>
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</table>

Infections can be divided into opportunistic infections (OI) which implied infections usually observed in patients with cell-mediated immunity (CMI) defects (the infections with nontuberculous mycobacterium, *Histoplasma capsulatum*, *Cryptococcus neoformans*, *Talaromyces marneffei*) and non-OI caused by *Salmonella* group, group A streptococcus, *Burkholderia pseudomallei* and *Mycobacterium tuberculosis*. The OR<sub>adj</sub> after adjusting for possible confounders time, sex, age and the presence of underlying diseases for occurrence of all infections if ND were present was 14.79 relative to those without ND. The OR<sub>adj</sub> of OI in the presence of ND was 12.35 whereas the OR for non-OI was considerably lower (1.52).

OR<sub>adj</sub> unadjusted odd ratio, OR<sub>adj</sub>-adjusted odd ratio, *p<0.25*, *p<0.05*, **p<0.01**, ***p<0.001*. 

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Cutaneous involvements have been reported in 49–57% of patients in other case series (3, 14, 15). Type of reactive dermatoses keep with our findings, being mainly ND. A slightly higher prevalence that is noted in the present study may be due to a long follow-up period. Of note, diffuse plane xanthoma (DPX) has never been reported to be a feature of the syndrome. DPX is a rare, non-inherited condition in which the patient can either have a normal or abnormal serum lipid level. In contrast with other forms of xanthomas, it is often associated with systemic diseases, especially hematological, principally monoclonal gammopathies or lymphoproliferative disorders (16, 17). There was a patient who had polyclonal gammopathy which may be secondary to infections as a complication of autoantibody to IFN-γ (17). However, this single case of DPX may be incidental. A longer follow-up period and more cases are needed to substantiate this association.

A guideline for treatments of reactive dermatoses in the syndrome has not yet been established. Most treatment options reported in the literature rely on immunosuppressive drugs, namely corticosteroid. Others including colchicine, dapsone, acitretin and calcitriol have all been used with variable results (7). In addition, if systemic infections are concurrently detected with reactive skin lesions, antibiotics and antimiycobacterial treatments should be instituted promptly (7). Treatment regimens given to patients in our series are in accordance with those of previous reports and clinical improvements were observed. However, one should critically weigh the risks and benefits of immunosuppressive therapies in patients who are susceptible to infections. Interestingly, favorable therapeutic responses in cases with refractory systemic infections with rituximab, a monoclonal anti-CD20 antibody have been reported (18, 19).

IFN-γ is produced mainly by activated T helper 1 (TH1) cells, natural killer (NK) cells, natural killer T (NKT) cells, and CD8+ T cells (20, 21). It is a critical cytokine involved in IFN-γ, interleukin (IL)-12, and tumor necrosis factor (TNF)-α axis that is primarily responsible for the containment of mycobacteria and intracellular pathogens (1, 22, 23). Autoantibodies to IFN-γ found in patients with the syndrome exhibiting neutralizing activity that can inhibit IFN-γ-dependent signal transducer and activator of transcription (STAT)1 phosphorylation thus predispose those patients with susceptibility to infections with normally considered low virulence pathogens (1). One would expect to observe some type of atopiform dermatitis in patients with derangement of TH1 function. However, only a single case with generalized papulovesicles on the trunk and extremities with histology showing superficial perivascular infiltration with eosinophils was found.

ND encompasses a group of disorders that are typified by neutrophilic infiltration into the skin and a possibility of extracutaneous infiltration, overlapping and interchangeable clinical features among disorders, and frequent association with systemic illness (9). The prevalence of ND in this cohort was higher than in other patients with opportunistic infections. For instance, ND is not commonly observed in NTM infections (3, 24, 25). Moreover, it is rarely reported in HIV infected individuals (26–28). Until recently, ND has been reported to be found in NTM patients affected by this syndrome (1, 3, 14, 15). The exact pathogenesis of ND remains to be elucidated. However, an increase in level of proinflammatory cytokines and chemokines, autoimmunity and aberration of neutrophils functions and clonality have been hypothesized as underlying causes (10).

We speculate that ND in this group of patients may be a result of the compensatory hyperactivation of innate immune responses to combat intracellular infections in patients with severely impaired CMI. This might explain the association of ND during occurrence of the OI, i.e. NTM, an infection due to Talaromyces marneffei and histoplasmosis that was not in the non-OI group. Furthermore, immune dysregulation of IL-23/Th17 axis, similar to that of pustular psoriasis and acute generalized exanthematosus pustulosis (AGEP) may also be responsible for increased neutrophils recruitment, activation and/or survival in the skin in these patients (29). Further studies are needed to verify this hypothesis. Nonetheless, there exists different immunologic mechanisms to counterbalance CMI defects in patients with the syndrome compared to that of AIDS, as evidenced by the fact that reactive ND skin lesions are not commonly found in HIV-infected individuals.

A potential limitation is the retrospective nature of our study. However, a thorough check of the data revealed only a small amount of missing values. Moreover, it will be interesting to examine whether higher titers of anti-IFN-γ autoantibody is associated with disseminated and/or opportunistic infections, and human leukocyte antigen (HLA) type of the patients. Unfortunately, these data were not available. Thus, further studies are needed to clarify these important points. Nevertheless, due to a long-follow up period and several visits, we can assess the temporal relationship of reactive ND with the existence of infections in patients. This information will be useful to dermatologists and/or internists monitoring patients.

In conclusion, we herein report detailed clinical, histological, laboratory, treatments and the significance of cutaneous involvements in adult-onset immunodeficiency due to anti-IFN-γ autoantibody. Skin findings are exceedingly common in this patients group. Moreover, they can signal systemic infections warranting physicians’ attention. Prompt diagnosis and correct treatment for infections may lead to decreased morbidity and mortality associated with these diseases.
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The authors have no conflicts of interest to declare.

REFERENCES


