Interstitial Granulomatous Dermatitis Associated With the Use of Tumor Necrosis Factor α Inhibitors

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Background: Tumor necrosis factor α (TNF-α) has been implicated in the pathogenesis of numerous inflammatory and autoimmune disorders. Accordingly, TNF-α inhibitors, such as thalidomide, infliximab (Remicade), adalimumab (Humira), and etanercept (Enbrel), have been used with success in the treatment of autoimmune disorders, including psoriasis, rheumatoid arthritis, inflammatory bowel diseases, and lymphoproliferative disorders. Although anti–TNF-α therapy is safe and well tolerated, various adverse cutaneous reactions have been reported.

Observations: We encountered 5 patients who developed erythematous annular plaques on the trunk and extremities while receiving 4 different medications with inhibitory activity against TNF-α. One patient was treated with lenalidomide (Revlimid) for multiple myeloma, 2 received infliximab, and 1 received etanercept for severe rheumatoid arthritis; the last patient was in a clinical trial of adalimumab for psoriatic arthritis. Skin biopsy specimens revealed diffuse interstitial granulomatous infiltrates of lymphocytes, histiocytes, and eosinophils, palisading degenerated collagen. Withdrawal of the medications led to complete resolution of the skin lesions.

Conclusion: Interstitial granulomatous dermatitis should be considered in the differential diagnosis of skin lesions occurring in the setting of anti–TNF-α therapy.

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Myeloma in 1. The characteristics of the skin lesion included rapid-onset asymptomatic to mildly pruritic skin rashes, manifested as multiple macules or indurated papules or plaques, 1 to 4 cm, mostly in annular configurations, some with a clear center and slightly elevated borders (Figure 1). The lesions were located on the trunk, shoulders, and upper extremities. In 3 patients, the rash developed within 1 to 3 months following initiation of the drug; and in 2 patients, the rash did not occur until more than 1 year after initiation of the drug. The clinical differential diagnosis included granuloma annulare and erythema multiforme. The eruption cleared in 3 patients and improved in 1 patient within 2 months on discontinuation of the TNF-α/H9251 inhibitors. In 1 patient (patient 4), the TNF-α/H9251 inhibitor could not be terminated because of her severe condition of RA, and skin lesions persisted at 3 months’ follow-up.

The histopathological features of the skin biopsy specimens from these patients are summarized in Table 2. Most patients had a diffuse interstitial granulomatous infiltrate in the mid and deep dermis. The infiltrate was composed of predominantly lymphocytes and histiocytes, with palisading around partially degenerated collagen, forming ill-defined to discrete foci of granulomas. There were a few to numerous eosinophils and scattered neutrophils and multinucleated giant cells (Figure 2). A mild interface and superficial perivascular infiltrate of lymphocytes were present in 2 patients. Neither dermal mucin nor neutrophilia was prominent. No vasculitis was observed, nor was there subcutaneous tissue involvement.

Immunophenotyping performed on 1 specimen (patient 1) demonstrated predominantly monocytes positive for CD14 (a toll-like receptor 4 accessory glycoprotein expressed by monocytes and macrophages) and CD4/H11001 and CD3/H11001 T lymphocytes, which were HLA-DR/H11001. Immunofluorescence studies performed on 1 specimen (patient 3) revealed IgM and C3 deposition within the small blood vessels in the papillary dermis and IgM deposits at the basement membrane zone. Keratinocytes showed focal cytoplasmic staining with IgA and IgG.

Lenalidomide is a derivative of thalidomide and is undergoing phase 2 clinical trials for the treatment of multiple myeloma. Lenalidomide works by enhancing the activation of T lymphocytes and natural killer cells. It is more potent than thalidomide in terms of its inhibitory activity against TNF-α/H9251. To our knowledge, adverse cutaneous reactions due to lenalidomide have not been reported. Infliximab is a chimerical anti–TNF-α monoclonal IgG1 kappa antibody. Infliximab binds to soluble TNF-α in the serum and blocks TNF-α bound to its receptors on target cells. Although safe and well tolerated, various adverse cutaneous reactions associated with infliximab are documented in the literature. These include leukocytoclastic vasculitis,urticaria, lichenoid eruption, discoid lupus erythematosus–like eruption, chill-

| Table 1. Summary of the Clinical Presentation of the 5 Patients |

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Disease</th>
<th>Drug</th>
<th>Time the Drug Was Discontinued and the Lesion Resolved, mo</th>
<th>Location of Disease</th>
<th>Description of Skin Lesion</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/55 MM</td>
<td>MM</td>
<td>Lenalidomide (Revlimid)</td>
<td>2</td>
<td>Back and proximal ETs</td>
<td>Mildly pruritic annular papules; some are targetoid</td>
<td>Resolved, and drug therapy discontinued</td>
</tr>
<tr>
<td>2/M/48 RA</td>
<td>RA</td>
<td>Infliximab (Remicade)</td>
<td>1</td>
<td>Back and shoulders</td>
<td>Generalized pruritic annular nodules and plaques; some have raised borders</td>
<td>Improved, and drug therapy discontinued; patient lost to follow-up</td>
</tr>
<tr>
<td>3/F/65 RA</td>
<td>RA</td>
<td>Infliximab</td>
<td>18</td>
<td>Flank and forearm</td>
<td>Erythematous macules/plaques with elevated borders</td>
<td>Resolved, and drug therapy discontinued</td>
</tr>
<tr>
<td>4/F/34 RA</td>
<td>RA</td>
<td>Etanercept (Entrel) and methotrexate</td>
<td>3</td>
<td>Elbows</td>
<td>Nonpruritic hyperpigmented papules</td>
<td>Etanercept therapy continued, and lesions persist</td>
</tr>
<tr>
<td>5/M/54 PA</td>
<td>PA</td>
<td>Adalimumab (Humira) and methotrexate</td>
<td>12</td>
<td>Thighs and back</td>
<td>Annular erythematous papules, nonpruritic</td>
<td>Resolved, and adalimumab therapy discontinued</td>
</tr>
</tbody>
</table>

Abbreviations: ET, extremity; MM, multiple myeloma; PA, psoriatic arthritis; RA, rheumatoid arthritis.

**COMMENT**

Lenalidomide is a derivative of thalidomide and is undergoing phase 2 clinical trials for the treatment of multiple myeloma. Lenalidomide works by enhancing the activation of T lymphocytes and natural killer cells. It is more potent than thalidomide in terms of its inhibitory activity against TNF-α. To our knowledge, adverse cutaneous reactions due to lenalidomide have not been reported. Infliximab is a chimerical anti–TNF-α monoclonal IgG1 kappa antibody. Infliximab binds to soluble TNF-α in the serum and blocks TNF-α bound to its receptors on target cells. Although safe and well tolerated, various adverse cutaneous reactions associated with infliximab are documented in the literature. These include leukocytoclastic vasculitis, urticaria, lichenoid eruption, discoid lupus erythematosus–like eruption, chill-
Etanercept is 100% human molecule composed of 2 recombinant p75 extracellular receptors fused to the Fc region of human IgG1. Etanercept competitively binds TNF-α/H9251 and TNF-β/H9252.6,7 Cases of leukocytolytic vasculitis, urticarial rash, pancytopenia, and aplastic anemia have been reported with etanercept use.8-10 In addition, patients are susceptible to opportunistic infections and reactivation of tuberculosis. Adalimumab is another genetically engineered fully human IgG monoclonal antibody that is a TNF-α inhibitor with a high specificity and affinity. It is being investigated for use in psoriasis and psoriatic arthritis, and is approved for RA. The adverse effects reported are injection site pain, local reaction, nausea, and upper respiratory tract infections.5

Interstitial granulomatous dermatitis (IGD) has been associated with various systemic disorders, most commonly RA, lupus erythematosus, systemic vasculitis, and lymphoproliferative disorders.11-15 Various names have been used to designate this entity, including IGD with arthritis, atypical granuloma annulare, linear granuloma annulare, and Churg-Strauss granuloma. Clinically, some patients develop linear cords or plaques on the lateral aspect of the trunk or extensor extremities; however, the clinical lesions may be variable. Histological examination results demonstrate IGD characterized by a diffuse infiltration of the interstitium by histiocytes, piecemeal fragmentation of collagen, and the formation of small granulomas around degenerative areas in concert with variable numbers of polymorphic leukocytes scattered within the infiltrate. Palisaded neutrophilic and granulomatous dermatitis was used in recent literature16 as the favored term to unify the previously mentioned names and to designate an entity of unusual cutaneous manifestation of various collagen vascular diseases, so-called immune complex disorders. It has been postulated that the deposition of immune complexes in dermal vessels serves as the inciting event, followed by activation of the complement and neutrophils and subsequent damage to dermal collagen. A granulomatous infiltrate is the secondary response to damaged collagen in the dermis.16

Magro et al17 described the first group of patients with IGD induced by various medications, particularly calcium channel blockers, lipid-lowering agents, angiotensin-converting enzyme inhibitors, antihistamines, anticonvulsants, and antidepressants. Subsequent reports18,19 on

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Description of the Infiltrate</th>
<th>MNGCs</th>
<th>Eos</th>
<th>PMNs</th>
<th>Mucin</th>
<th>Immunophenotyping</th>
<th>DIF Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Diffuse interstitial granulomatous infiltrate in the mid and deep dermis</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>CD14+, CD4+</td>
<td>ND</td>
</tr>
<tr>
<td>2</td>
<td>Diffuse interstitial infiltrate in the mid dermis</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>3</td>
<td>Interstitial and discrete foci of granuloma in the mid and deep dermis</td>
<td>++</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>ND</td>
<td>IgM and C3 in BVs and IgM in the BMZ</td>
</tr>
<tr>
<td>4</td>
<td>Diffuse interstitial granuloma in the mid and deep dermis</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>5</td>
<td>Diffuse interstitial infiltrate in the deep dermis</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>-</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

Abbreviations: BMZ, basement membrane zone; BV, blood vessel; DIF, direct immunofluorescence; Eos, eosinophils; MNGC, multinuclear giant cell; ND, not done; PMN, polymorphic neutrophil; +, scattered; ++, frequent; +++, numerous; -, absent.

*In all 5 patients, lymphocytes were frequent and histiocytes were numerous.
IGD induced by other drugs have been published. Clinically, patients developed annular erythematous-violaceous plaques on the arms, medial thighs, and intertriginous areas. Defining histopathological features included an interstitial lymphohistiocytic infiltrate, fragmentation of collagen and elastic fibers, a variable amount of mucin deposition, interface changes, lymphoid atypia, and eosinophils. Necrobiosis and vasculitis were characteristically absent. Extravascular neutrophilia with leukocytoclasia was not a feature. The absence of neutrophils is thought to be a cardinal feature that differentiates an interstitial granulomatous drug reaction from other causes of IGD.

It is likely that IGD represents a reactive phenomenon with a histopathological spectrum, which arises in conjunction with various disorders, including autoimmune diseases, lymphoproliferative disorders, and drug reactions. Depending on the stage when biopsy specimens are obtained, the composition of the cellular infiltrates may vary in terms of the numbers of neutrophils, lymphocytes, and eosinophils and by the presence or absence of vasculitis. The underlying pathogenesis may be related to an immune complex disorder and subsequent ischemia and collagen degeneration, as hypothesized by Chu et al.16

All patients described herein developed IGD while taking medications with inhibitory activity against TNF-α. Of the 5 patients, 3 had underlying RA, 1 had psoriatic arthritis, and 1 had multiple myeloma. Patients with the previously mentioned diseases, particularly RA, are known to have granulomatous diathesis.13-16 However, the close association between the development of skin lesions after the initiation of anti–TNF-α therapy and, most importantly, the clearance or improvement of the skin lesions on discontinuation of TNF-α inhibitors suggests a role for the medication and the development of cutaneous lesions.

Recently, Bremner et al17 reported on 4 cases of palisaded neutrophilic and granulomatous dermatitis. Interestingly, 3 of the 4 cases were patients with RA receiving treatment with infliximab. Although the authors disregarded the direct role of the TNF-α antibody, infliximab, in the patient's skin eruption because of lack of support in the literature, the fact that all 3 patients developed palisaded neutrophilic and granulomatous dermatitis while taking infliximab calls for further exploration of the temporal relationship between the development of skin lesions and anti–TNF-α therapy. Unlike our patients, the anti–TNF-α antibody was not discontinued in those patients and the lesions persisted despite treatment with systemic corticosteroids and other therapies.

Anti–TNF-α therapy is not the first treatment to be associated with IGD in patients who have underlying RA. Cutaneous and pulmonary granulomatous disorder triggered by methotrexate in a patient with RA has been reported.21 It is possible that anti–TNF-α agents enhance the likelihood of developing IGD in RA patients who have granulomatous diathesis, although the true incidence of IGD in RA patients with or without anti–TNF-α therapy is not known. Further studies will be necessary to answer these questions.

The main differential diagnosis, from a clinical and histopathological standpoint, is granuloma annulare, a self-limited disorder that generally lacks association with systemic diseases, although generalized granuloma annulare associated with systemic diseases such as diabetes mellitus has been reported. Granuloma annulare is commonly seen in young patients presented with annular plaques on the dorsal aspects of the extremities. Histologically, the lesion shows a top-heavy infiltrate of histiocytes that tend to form discrete foci. Necrobiosis, dermal mucin deposition, and multinucleated giant cells are frequently present. Neutrophils are generally absent. Because it is well known that patients undergoing anti–TNF-α therapy have an increased risk of infection with mycobacterium tuberculosis, either primary activation or reactivation of latent infections,22 tuberculosis should be considered in the differential diagnosis. Special stains and tissue culture should be ordered if an infectious cause is suspected.

In summary, to our knowledge, we described the first series of IGD in patients receiving 4 different TNF-α inhibitors. Among the 5 patients, 3 had RA. Withdrawal of the medication led to resolution of the skin lesions. Thus, IGD should be considered in the differential diagnosis of annular lesions occurring in the setting of anti–TNF-α therapy.

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Previous Presentation: This study was presented in part at the 41st Annual Meeting of the American Society of Dermatopathology; October 15, 2004; Boston, Mass.

REFERENCES
Announcement

Identifiable Patient Photographs

Please do not send masked photographs of patients.1

Until the late 1980s, placing black bars over the eyes of patients was accepted as a way to mask the identities of patients in photographs when consent to publish their photographs was not or could not be obtained. However, bars across eyes do not always mask identities and should not be used. . . . Therefore, when photographs of faces or identifiable body parts or detailed case descriptions are included in a manuscript, authors should obtain written permission from the identifiable subject (or a legally authorized representative) to publish the photograph or case description, and send a copy of the permission to the journal.

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