Granulomatous drug reactions from targeted therapeutics including biologics and small molecule inhibitors

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Abstract
Granulomatous drug reactions have been associated with many medications, including targeted therapeutics such as biologics and small molecule inhibitors. The four main clinicopathologic reaction patterns are drug-induced sarcoidosis-like reaction, reactive granulomatous dermatitis, granuloma annulare, and accelerated rheumatoid nodulosis. These reactions often develop months after exposure to the causative medication and clinically can mimic other granulomatous diseases or metastatic cancer, which may be differentiated with biopsy, tissue culture, and radiographic imaging. Granulomatous inflammation may be limited to the skin, where early recognition helps to facilitate diagnosis. Cutaneous manifestations vary by reaction pattern, ranging from erythema nodosum-like lesions to painful rheumatoid nodules to annular indurated plaques. Systemic granulomatous inflammation is typically only observed in sarcoidosis-like reaction or accelerated rheumatoid nodulosis and most often involves the lungs or lymph nodes. Targeted therapeutics implicated in granulomatous drug reactions are TNFα inhibitors, BRAF and MEK inhibitors, immune checkpoint inhibitors and, to a lesser extent, other cytokine modulators. TNFα inhibitors, in particular, are among the most common drugs in any class associated with the four primary granulomatous drug eruptions. We review the current literature on granulomatous reactions to these agents, including proposed mechanisms and the range of clinical manifestations. Management may include drug discontinuation, topical therapy, or systemic immunosuppression depending on the severity of the granulomatous drug reaction. In the setting of malignancy, granulomatous inflammation does not appear to be of prognostic value, although more studies are needed.

1. Introduction

Granulomatous drug reactions (GRs) constitute a rare subgroup of non-infectious granulomatous diseases that are elicited by various classes of medications. GRs are distinguished from other granulomatous diseases by their temporal association with drug initiation, resolution or improvement with drug discontinuation, and recurrence with drug re-challenge. GRs are classified into four main reaction patterns with distinct clinicopathologic features (Table 1): drug-induced sarcoidosis-like reaction (SLR), reactive granulomatous dermatitis (RGD), granuloma annulare (GA), and accelerated rheumatoid nodulosis (ARN).[1] RGD is an umbrella term that consists of four subtypes: interstitial granulomatous, polycyclic (granuloma annulare-like), palisaded neutrophilic and granulomatous, and drug-induced. Note that drug-induced RGD can present like any other subtype but also includes interstitial granulomatous drug reaction.[2,3]

Table 1: Characteristic features of the four primary granulomatous drug eruptions[1,2]

Reaction pattern	Proposed pathophysiology	Typical cutaneous features*	Histological features	Systemic Manifestations	Commonly associated medications
Drug-induced sarcoid like reaction	Immune dysregulation promoting Th1 profile	Erythema nodosum, indurated papules and plaques	Epithelioid non-caseating granulomas	Possible lung, lymph node, eye, salivary gland, joint, nervous system, liver, heart, or kidney involvement	TNFα inhibitors, Immune checkpoint inhibitors, Interferon-α, BRAF and MEK inhibitors
Drug-induced reactive granulomatous dermatitis	Alterations in dermal collagen antigen potential	Erythematous to violaceous annular plaques in intertriginous areas	Interstitial histiocytes surrounding fragmented collagen +/- vacuolar interface dermatitis, eosinophils, lymphoid atypia	Not described	Calcium channel blockers, TNFα inhibitors, ACE inhibitors
Drug-induced granuloma annulare	Immune dysregulation	Generalized annular erythematous papules or plaques	Increased dermal mucin, interstitial histiocytes or palisading histiocytes surrounding degenerated collagen	Not described	TNFα inhibitors
Drug-induced accelerated rheumatoid nodulosis	Genetic predisposition from polymorphisms in HLA DRB1, methionine synthase reductase gene, adenosine and folate pathways[91]	Rapid onset of indurated, painful, sometimes ulcerated nodules on the hands in a patient with seropositive, erosive rheumatoid arthritis	Similar to rheumatoid nodules: palisading granuloma with histiocytes surrounding fibrinoid necrosis	Possible lung, heart, or brain involvement	Methotrexate, TNFα inhibitors

*Many clinical variations have been reported

Diagnosis of these entities is often challenging. Delays of months to years between drug initiation and GR presentation, during which patients often start and stop numerous other medications, create difficulties in identifying the causative agent. Clinical presentations are variable, mimicking other granulomatous diseases including infections which must be excluded. Further, some GRs are limited to the skin, while others involve multiple organs. In patients undergoing treatment for cancer, GRs may be mistaken for metastatic disease. It is vital for the clinician to be aware of these distinctions in order to guide diagnosis and management. Radiographic imaging, tissue culture, and biopsy—including special stains for infectious organisms or cancer markers— are often helpful in the diagnostic evaluation.

As use of targeted therapies such as biologics and small molecule inhibitors continues to expand, so do reported associations with GRs. The most commonly implicated agents are TNFα inhibitors, BRAF and MEK inhibitors, and immune checkpoint inhibitors. GRs associated with other cytokine modulators are not as well characterized, including inhibitors of IL-1, IL-6, IL-12, IL-17, and IL-23. This article reviews GRs caused by targeted therapeutics, discussing their cutaneous manifestations, systemic associations, and management.

2. TNFα inhibitors

TNFα is a pro-inflammatory cytokine involved in granuloma formation and maintenance. TNFα inhibitors— including etanercept, adalimumab, and infliximab— have been used successfully in some treatment-refractory granulomatous diseases. Patients with cutaneous sarcoidosis who have failed first and second line treatments such as corticosteroids, methotrexate, azathioprine, and hydroxychloroquine, demonstrated

clinical improvement with TNFα inhibitors.[4] Case reports suggest that TNFα inhibitors may also be effective in granuloma annulare, interstitial granulomatous dermatitis, and necrobiosis lipoidica.[5-7]

In certain patients, however, TNFα inhibitors paradoxically incite granulomatous inflammation. The underlying mechanism remains unclear, although some patients treated with TNFα inhibitors show increased IFN-γ and TNFα production by T cells.[8] Specific TNF polymorphisms may predict TNFα inhibitor efficacy,[9,10] and theoretically, propensity for adverse effects. Thus, in certain genetically-predisposed individuals, TNFα inhibitors may disrupt cytokine balance and promote a Th1 response that facilitates granuloma formation.

Drug-induced SLR is the most widely reported paradoxical granulomatous reaction to TNFα inhibitors. A literature review of 82 cases reported that SLR developed on average 24 months after TNFα inhibitor initiation (range 1-84 months).[11] TNFα inhibitors have been reported to cause cutaneous sarcoidosis as well as pulmonary sarcoidosis, ocular sarcoidosis, and neurosarcoidosis, according to a query of individual case safety reports collected from the World Health Organization pharmacovigilance database.[12] In this study, TNFα inhibitors were the most frequent trigger of SLR (most commonly etanercept, followed by infliximab and adalimumab). Other reviews have also described extracutaneous sarcoidosis induced by TNFα inhibitors, most commonly involving the lungs or lymph nodes,[13,14] and less commonly the liver, eyes, salivary glands, central nervous system, or bone marrow. In a literature review of 34 cases of SLR induced by TNFα inhibitors, 32% had cutaneous manifestations, often presenting as erythema nodosum-like lesions.[14] 32 of 33 patients who

discontinued the causative drug noted complete clearance in an average of 5.2 months.[14] In another study, 60% of patients required additional anti-sarcoidosis therapy for management.[11]

While classically associated with methotrexate therapy,[1] accelerated rheumatoid nodulosis has also been reported in patients on etanercept,[15-20] adalimumab,[16,21] infliximab,[16,22] and golimumab.[23] ARN usually occurs in patients with seropositive RA, most of whom report significant improvement in disease activity with TNFα inhibitors. ARN developed an average of 16 months (range 2-48 months) after drug initiation in the reviewed cases. Cutaneous ARN commonly occurs on the dorsal hands or elbows. In three patients, onset of rheumatoid nodulosis correlated with a flare in articular disease.[17,20,21] Importantly, several reported patients developed pulmonary rheumatoid nodulosis, sometimes in the absence of cutaneous disease.[15-18,20,23] In some patients with pulmonary rheumatoid nodulosis, pulmonary disease stabilized or improved after TNFα inhibitor discontinuation,[15,17,18,20,23] while others remained on the medication with no evidence of pulmonary disease progression.[16,19]

In a chart review of 199 patients with seropositive RA treated with TNFα inhibitors, nine developed disseminated GA on the forearms or hands.[24] Six had been treated with adalimumab, two with infliximab, and one with etanercept. Average time of occurrence was 8 months after drug initiation (range 3-14 months). In two patients, the TNFα inhibitor was discontinued, while the seven remaining patients responded well to topical corticosteroids which allowed drug continuation. Of note, 127 patients with

spondyloarthropathies were also reviewed, none of whom developed GA.

Reactive granulomatous dermatitis has been reported in association with etanercept,[25-27] adalimumab,[25,28,29] infliximab,[25,30] and lenalidomide[25] used to treat RA, juvenile idiopathic arthritis, psoriatic arthritis, and multiple myeloma. Cutaneous manifestations were variable, ranging from violaceous annular plaques to tender indurated nodules on the trunk or extremities. Onset ranged from weeks to years, and there were no reports of systemic involvement. Some improved with topical corticosteroids alone,[26,27] while in other patients drug discontinuation led to resolution.[25,28,29,31]

Notably, some patients who developed a granulomatous reaction to one TNFα inhibitor reported improvement after switching to another one.[13] There are reports of etanercept-induced pulmonary sarcoidosis resolving with adalimumab,[32] and vice versa.[33] Wallis and Ehlers proposed that differences in infliximab and etanercept granulomatous therapeutic activity may be explained by distinct binding affinities for soluble and transmembrane TNFα, binding kinetics, and rates of apoptosis.[34] While infliximab binds TNFα irreversibly, etanercept associates and dissociates rapidly, and may permit enough TNFα activity for granuloma formation. Indeed, randomized controlled trials show that etanercept is not effective for granulomatous diseases like Crohn's disease[35] or pulmonary sarcoidosis.[36]

3. Protein kinase inhibitors

GRs related to protein kinase inhibitors are most frequently seen in patients with metastatic melanoma treated with BRAF inhibitor monotherapy or BRAF and MEK inhibitor combination therapy. BRAF and

MEK inhibitors may mediate granuloma formation through increased serum levels of TNFα and IFN- γ[37] in addition to promoting melanoma antigen presentation, PDL1 expression, and CD8+ T-cell infiltratation.[38] Park et al. theorized that GRs may result from treatment-mediated immune activation against melanoma cell targets.[39] In their case series, one patient who developed a GR on dabrafenib and trametinib was biopsied to show MART-1 and MITF positive melanoma cells at the center of the granulomatous inflammation. In many other cases, however, no melanoma was identified in biopsied granulomas.[40-42]

In our review of the literature, 30 patients developed SLRs in response to BRAF inhibitor monotherapy or BRAF and MEK inhibitor combination therapy.[5,39-53] The average onset was 9 months after drug initiation (range 1-21).[5,39-53] 25 (83%) had cutaneous involvement, while 12 (40%) had systemic manifestations including granulomatous inflammation of the lungs,[43,46] lymph nodes,[44] eyes,[43,44,52] liver,[51] kidney,[41] joints,[43,44] heart,[47] and salivary gland.[53]

In 8 patients, the targeted therapy was discontinued, due to granulomatous reaction severity,[41] patient preference,[50] cancer progression,[40,42] or completion of treatment.[54] SLRs were managed with topical corticosteroids only (63%, n=19), no specific treatment (20%, n=6), or systemic steroids (17%, n=5). In 20 patients (67%), the SLR completely resolved, including in 7 who had stopped targeted therapy. The SLR in 4 (13%) patients partially responded to treatment, 2 (7%) stabilized, and 3 (10%) progressed, resulting in death in one patient due to granulomatous myocarditis.

Tumor response was reported in 26 patients with SLR: 12 (46%) had a complete response, 3 (12%) a partial response, 1 (4%) stabilized, and 10 (40%) had progressive disease. In comparison, Huynh et al. reported 63 patients treated with dabrafenib and trametinib for stage III or IV melanoma, 7 of whom developed SLRs.[53] 3 (42%) of these patients ultimately achieved complete melanoma remission, while 4 (57%) experienced progressive disease. Rates of melanoma progression were similar in their total cohort of 60 patients on targeted therapy with reported disease prognosis: 23 (38%) achieved complete remission, partial remission, or stable disease while 37 (62%) progressed. Although limited, these data do not suggest a clear association between SLR development and the likelihood of progression-free survival in melanoma patients treated with BRAF or MEK inhibitors.

BRAF and MEK inhibitors have also been associated with a few cases of drug-induced GA[55-57] and granulomatous panniculitis.[58,59] Other subclasses of protein kinase inhibitors have been described in single cases of reactive granulomatous dermatitis, including sorafenib, a multikinase inhibitor, in a patient with hepatocellular carcinoma,[60] bosutinib, a BCR-ABL tyrosine kinase inhibitor, in a patient with chronic myelogenous leukemia,[61] and trastuzumab, a HER2 inhibitor, in a patient with breast cancer.[62]

4. Immune checkpoint inhibitors

Immune checkpoint inhibitors include antagonists of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), programmed death 1 (PD-1), and programmed death ligand 1 (PD-L1). These agents inhibit tumor-mediated blockade of T cells, restoring immune system antitumor activity. Immune-related adverse events include granulomatous inflammation, perhaps

mediated by increased circulating Th17 cells.[63]

Cornejo et al. reviewed 72 patients with GRs to immune checkpoint inhibitors reported in the literature through June 2018.[64] 59 patients presented with SLR, 4 with granulomatous panniculitis, 4 with GA, 4 with granulomatous dermatitis, and 1 with granulomatous foreign body reaction. SLR occurred most frequently in patients treated with PD-1 (59%) or CTLA-4 (34%) inhibitors. After an average of 5.6 months (range, 0-24 months),[64] patients commonly presented with granulomatous inflammation of the lungs (85%) or skin (49%), and more rarely, eyes or thyroid. Pulmonary involvement was often asymptomatic or accompanied by mild cough or dyspnea. Immunotherapy was discontinued in 49% of patients (25 of 51), 57% received systemic steroids (29 of 51), and 24% received topical or no therapy (12 of 51). With this management, 94% of all SLR cases resolved. Of the 35 patients for whom tumor response was reported, 15 (43%) achieved partial or complete response, 7 (20%) had stable disease, and 13 (37%) experienced disease progression.

In the four patients with drug-induced GA, no systemic involvement was reported. GA was managed with partial response to systemic or topical steroids, and resolved completed after immunotherapy was completed. All patients for whom tumor status was reported had achieved a complete or partial response.[64]

More recently, Chorti et al. reported 10 patients with SLR in their cohort of 45 patients treated with adjuvant nivolumab alone or in combination with ipilimumab for stage III melanoma.[65] Asymptomatic mediastinal or hilar lymphadenopathy was the most common presentation (8 of 10), detected on routine radiographic imaging after a median of 2.8 months. Lung, skin, and bone involvement were also reported. SLRs resolved or stabilized in all patients, 3 of whom had discontinued immunotherapy. Melanoma progression occurred in equal frequency in patients with or without SLR: 2 of 10 patients (20%) with SLR and 7 of 35 patients (20%) without SLR.

5. Other cytokine modulators

Various other cytokine inhibitors have been associated with GR, albeit far less frequently than TNFα inhibitors.

The IL-1 receptor antagonist anakinra has been reported in two cases each of SLR[66,67] and reactive granulomatous dermatitis[68,69] in the setting of rheumatoid arthritis,[68] hidradenitis suppurativa,[66] TNF receptor-associated periodic syndrome,[67] and diffuse large B cell lymphoma.[69] IL-1R antagonists may mediate granuloma formation via unopposed type I IFN- γ activity favoring a Th1 profile.[66] One case of SLR had systemic involvement of the eyes, joints, mediastinal lymph nodes, and salivary glands.[67] Average onset was at 12 months after drug initiation (range 0-24). Skin manifestations included pink papules and plaques, sometimes tender, on the trunk. In three cases, anakinra was discontinued with complete GR resolution[66,68,69]. In the remaining case, anakinra was continued and the SLR resolved within one month of systemic steroids.[67]

The IL-6 receptor inhibitor tocilizumab has been proposed as a third-line option for treatment-refractory sarcoidosis,[70] although tocilizumab may paradoxically promote GR in certain patients in part due to dysregulation of regulatory T cells.[70,71] SLRs to tocilizumab have been described in three patients, two with RA[72,73] and one with giant cell arteritis,[74] after an average of 17 months. One patient had involvement of the hilar and

mediastinal lymph nodes, for which tocilizumab was discontinued and the patient received systemic steroids with complete resolution.[72] The remaining two patients with cutaneous sarcoidosis were successfully treated with topical steroids and were able to continue tocilizumab.[73,74] There are two reported cases of GA associated with tocilizumab in one patient with RA[75] and one with neuromyelitis optica[71] after an average of 4.5 months. In one patient, GA resolved with tocilizumab discontinuation and systemic steroids.[75] In the other, tocilizumab was continued and GA resolved with topical steroids.[71] Finally, one report described accelerated rheumatoid nodulosis associated with tocilizumab in 5 patients, although 3 of these patients were concurrently treated with methotrexate and the remaining 2 had received methotrexate and a TNF inhibitor in the recent past.[76]

Ustekinumab is a IL-12 and 23 inhibitor which has been associated with three cases of SLR in patients with psoriasis.[77-79] All patients had systemic involvement of the lymph nodes, lungs, bones, liver, or spleen, and only one had cutaneous manifestations presenting as erythema nodosum-like lesions. Ustekinumab was discontinued and systemic steroids started in all patients. Interestingly, in a clinical trial, ustekinumab was not shown to be effective in the treatment of cutaneous or pulmonary sarcoidosis.[80]

Two patients treated for psoriasis with the IL-17A inhibitor secukinumab developed GA an average of 3.5 months after drug initiation.[81,82] Both cases improved partially with drug discontinuation, and one resolved after switching to etanercept.[82] Recently, 3 cases of SLR have been described in association with secukinumab.[83] One patient had cutaneous sarcoidosis at baseline that worsened within a month of starting secukinumab, and the other two presented with systemic involvement of the spleen, lymph nodes, or lung. Wang et al. theorized that IL-17 blockade may promote granulomatous inflammation via downregulation of NOD2, a gene which when mutated may cause Blau syndrome or Crohn's disease.[84] Consistent with this hypothesis, secukinumab has been ineffective in clinical trials of Crohn's disease.[85]

6. Discussion:

GRs, including SLRs, RGD, GA, and ARN, are increasingly recognized adverse effects of targeted therapeutics, including biologics and small molecule inhibitors. These reactions have been observed most frequently in patients treated with TNFα inhibitors, BRAF and MEK inhibitors, and immune checkpoint inhibitors, although the list of implicated agents will likely continue to expand (Table 2).

Table 2: Targeted therapeutics associated with granulomatous drug eruptions

Drug-induced sarcoid-like reaction	Drug-induced reactive granulomatous dermatitis	Drug-induced granuloma annulare	Drug-induced accelerated rheumatoid nodulosis
TNFα inhibitors*	TNFα inhibitors*	TNFα inhibitors	TNFα inhibitors*
Immune checkpoint inhibitors*	IL-1R inhibitors	BRAF and MEK inhibitors	IL-6R inhibitor
BRAF and MEK inhibitors*	Multkinase inhibitor	Immune checkpoint inhibitors	
IL-17A inhibitors	BCR-ABL tyrosine kinase inhibitor	IL-17A inhibitors	
IL-12/23 inhibitors	HER2 inhibitor	IL-6R inhibitors	
IL-6R inhibitors			
IL-1R inhibitors			

*Over 10 reported cases to date

The pathophysiology of GR remains incompletely understood. Paradoxically, some targeted therapies associated with GRs have also been reported as successful treatment options for refractory granulomatous diseases. Inhibitors of TNFα and IL-6R, for example, may precipitate SLRs in some patients and improve sarcoidosis in others.[4,70] Granuloma formation is likely mediated by complex interactions of cytokine imbalance, immune cell modulation, and neoantigen presentation, perhaps in genetically-predisposed individuals.[8,9,37,38,63]

GR diagnosis is complicated by variable clinical presentations that may be mistaken for metastatic disease or other granulomatous diseases. Further, delays of months to years between drug initiation and GR development are typical. If a GR is suspected, biopsy should be performed to distinguish between granulomatous processes with similar clinical appearance or metastases. Other causes of granulomas must be excluded, particularly infectious etiologies like tuberculosis which may be seen more frequently when using certain targeted therapies. Radiographic imaging, tissue culture, and special stains on biopsy for infectious organisms or cancer markers are often helpful in clarifying the diagnosis.

As with any drug-induced adverse effect, the severity of the GR should be weighed against the potential therapeutic benefit when deciding whether to continue the implicated drug. Special considerations include possible systemic involvement and the severity of the underlying disease. The causative agent is more likely to be interrupted or discontinued when associated with SLR or ARN, as these reaction patterns may involve extracutaneous organ systems. In GA and RGD, on the other hand, the drug is often continued. Skin findings are usually managed topically, although sometimes systemic steroids or other immunosuppressants may be needed for more extensive disease. Switching to another medication within the same class is another consideration, particularly with TNFα inhibitors which may vary in their granulomatous potential.[34]

When using targeted therapies for cancer, it is important to consider whether GRs signify

a more robust antitumor response or improved clinical outcome, as does vitiligo in melanoma patients.[86] While there does not appear to be a clear relationship between GR development and progression-free survival in patients treated with BRAF, MEK, or immune checkpoint inhibitors, the current data is limited. Only small case reports and series describe GRs to targeted cancer therapies and tumor response. Comparisons across reports are confounded by differences in tumor stage and other baseline patient characteristics, as well as varied approaches to GR management. In some patients, cancer treatments are interrupted or discontinued. Others are treated with systemic immunosuppressants that may negatively affect cancer prognosis. For example, some studies suggest that systemic corticosteroids are associated with poorer survival outcomes.[87]

This review is limited by the rare nature of these reactions and the paucity of larger studies characterizing their development. In some cases, strong evidence that the targeted therapy elicited the GR is suggested by a temporal association between GR development and drug initiation, resolution with discontinuation, and recurrence with re-introduction. In other reports, however, the associations may be merely corollary. Perhaps GR development is stimulated by the tumor itself in some cases, or is completely independent of the underlying disease.

Tumor-related sarcoid reactions have been described in some malignancies including up to 4.4% of carcinomas, 13.8% of Hodgkin's disease, and 7.3% of non-Hodgkin's lymphoma.[88] These reactions are thought to be induced by antigens that are released by tumor cells, possibly during necrosis, which spread through the lymphatic system to incite an immunologic response.[89] At least one SLR has been reported in a treatment-naïve patient with malignant melanoma.[90]

In summary, targeted therapeutics are increasingly recognized causes of GRs, including SLRs, GA, ARN, and RGD. These reactions often develop months after exposure to TNFα, BRAF, MEK, immune checkpoint, and other cytokine inhibitors. The complex signaling pathways that facilitate granuloma formation are not fully elucidated, but likely involve an imbalance in cytokines and immune cells that favors a Th1 profile. Granulomatous inflammation may be limited to the skin, where early recognition and biopsy can expedite diagnosis. In SLRs and ARN, on the other hand, multiorgan involvement is often asymptomatic and may mimic metastatic disease or other granulomatous diseases. Further studies are needed to better characterize whether granulomatous inflammation is of prognostic value in the setting of malignancy. Correct diagnosis of these conditions is imperative in directing patient management.

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