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Drug-Induced Sarcoidosis-Like Reactions

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A drug-induced sarcoidosis-like reaction (DISR) is a systemic granulomatous reaction that is indistinguishable from sarcoidosis and occurs in a temporal relationship with initiation of an offending drug. DISRs typically improve or resolve after withdrawal of the offending drug. Four common categories of drugs that have been associated with the development of a DISR are immune checkpoint inhibitors, highly active antiretroviral therapy, interferons, and tumor necrosis factor-α antagonists. Similar to sarcoidosis, DISRs do not necessarily require treatment because they may cause no significant symptoms, quality of life impairment, or organ dysfunction. When treatment of a DISR is required, standard antisarcoidosis regimens seem to be effective. Because a DISR tends to improve or resolve when the offending drug is discontinued, this is another effective treatment for a DISR. However, the offending drug need not be discontinued if it is useful, and antigranulomatous therapy can be added. In some situations, the development of a DISR may suggest a beneficial effect of the inducing drug. Understanding the mechanisms leading to DISRs may yield important insights into the immunopathogenesis of sarcoidosis.

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KEY WORDS: drug-induced sarcoidosis-like reaction; immune checkpoint inhibitors; interferons; tumor necrosis factor antagonist

Several drugs have been associated with the development of syndromes indistinguishable from sarcoidosis that are described as drug-induced sarcoidosis-like reactions (DISRs). Because the exact immunopathogenesis of sarcoidosis is unknown, it is not clear if these drugs are truly causing sarcoidosis, rendering the immune system more susceptible to the development of sarcoidosis, exacerbating subclinical cases of sarcoidosis, or causing conditions that are distinct from sarcoidosis. Because a DISR may be confused with other clinical conditions, including infections, other drug reactions, and malignancies, it is important to recognize this disease entity because the misdiagnosis of a DISR may lead to unnecessary or inappropriate testing or treatment.

In this paper, we review our current understanding of DISRs including the known causative drugs, clinical features, prognosis, management, and potential mechanisms causing these reactions.

A comprehensive search query of medical databases was performed using a combination of appropriate subject headings and key words including "drug" and

ABBREVIATIONS: ART = antiretroviral therapy; ASIA = autoimmune inflammatory syndrome induced by adjuvants; CD = cluster of differentiation; CTLA-4 = cytotoxic T lymphocyte antigen-4; DISR = drug-induced sarcoidosis-like reaction; ICI = immune checkpoint inhibitor; IFN = interferon; irAE = immune-related adverse event; PD-1 = programmed death protein 1; Th = T-helper; TNF = tumor necrosis factor

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"sarcoidosis," and "drug" and "granuloma" ("drug induced sarcoidosis," "drug induced granulomatous reaction," "drug induced sarcoid like granulomatous reaction," and "drug induced sarcoidosis like reaction"). The search was executed in the MEDLINE, PubMed, Embase, Cochrane Library, and Web of Science databases from database inception through December 2017. Animal studies were excluded using the search statement recommended by the Cochrane Collaboration. Search results were independently screened by three reviewers (A. C., A. N., and M. A. J.). Data were obtained in the form of single case reports and case series published in the English literature.

Clinical Definition of a DISR

We define a DISR as a systemic granulomatous tissue reaction that is indistinguishable from sarcoidosis and occurs in a temporal relationship with initiation of an offending drug. To date, there is no clinical presentation that distinguishes a DISR from sarcoidosis, and both have been associated with bilateral hilar adenopathy,[1-4] cutaneous lesions,[5-7] uveitis,[3,8] granulomatous infiltration of scars,[1,9] hypercalcemia,[9] elevated serum angiotensin-converting enzyme levels,[1,3,8,10,11] and 18F-fluorodeoxyglucose uptake on PET scans.[2,11,12] Histopathologically, DISR granulomas completely resemble sarcoid granulomas with presence of noncaseating giant-cell epithelioid granulomas surrounded by lymphocytes, with occasional presence of birefringent foreign bodies, asteroid bodies, and Schaumann bodies.[7,13-15] Because it is possible that sarcoidosis could coincidentally occur soon after the administration of a drug, there is always a chance that a patient with a DISR truly has sarcoidosis. Unlike sarcoidosis, DISRs often resolve after discontinuation of the offending agent, and may recur with rechallenge; these may be the only features that reliably distinguish these two entities. A list of drugs clearly associated with DISRs is shown in Table 1.[3,4,6,7,10,12,15-145] In Figure 1, a case of a DISR is shown.

Similar to the diagnosis of sarcoidosis, the diagnosis of a DISR cannot be established unless alternative causes for granulomatous inflammation have been reasonably excluded (Table 2). Certain alternative causes require particular attention to exclude prior to establishing the diagnosis of a DISR. First, because many offending drugs that cause DISRs are immunosuppressive, a thorough search for granulomatous infections such as mycobacterial and fungal infections must be conducted. Second, because chemotherapeutic agents may cause a DISR, a sarcoidosis-like reaction of malignancy needs to be distinguished from a DISR in these cases. Sarcoidosis-like reactions of malignancy occur with lymphoproliferative malignancies and solid organ cancers.[146,147] The granulomatous inflammation with a sarcoidosis-like reaction of malignancy usually occurs in the cancerous organ, the draining lymph nodes of the cancerous organ, or in a cancerous metastasis. Although an immunohistochemical analysis is usually not performed, granulomas from sarcoid-like reactions of malignancy contain B lymphocytes and sinus histiocytes that are not observed in sarcoid granuloma, and this distinguishes these two entities.[146] Third, a DISR should be differentiated from acute granulomatous interstitial lung disease from methotrexate[148-150] and acute pulmonary granulomatosis with alveolar damage from intracavitary Bacillus Calmette-Guérin therapy.[151,152] These are isolated pulmonary toxicities, which are usually progressive, and may result in respiratory failure from pulmonary compromise. Finally, because many of the drugs associated with DISRs are injectable agents, a foreign body granulomatous reaction at an injection site

TABLE 1] Common Drugs Associated With Drug-Induced Sarcoidosis-Like Reactions

Drug Class	Drugs	No. of Patients	References
Immune checkpoint inhibitors	Ipilimumab	14	12, 16-21
	Nivolumab	4	7, 22-24
	Pembrolizumab	4	12, 25-27
Highly active antiretroviral therapy	…	23	28-36
Interferons	Interferon-alpha	99	6, 8, 10, 37-72
	Interferon-beta	9	73-78
Tumor necrosis factor-α antagonist	Etanercept	47	3, 15, 79-128
	Adalimumab	18	15, 79, 83, 100, 102, 107, 115, 121, 129
	Infliximab	17	15, 80-83, 130-137
Miscellaneous drug class	*BRAF* inhibitors	8	138-145

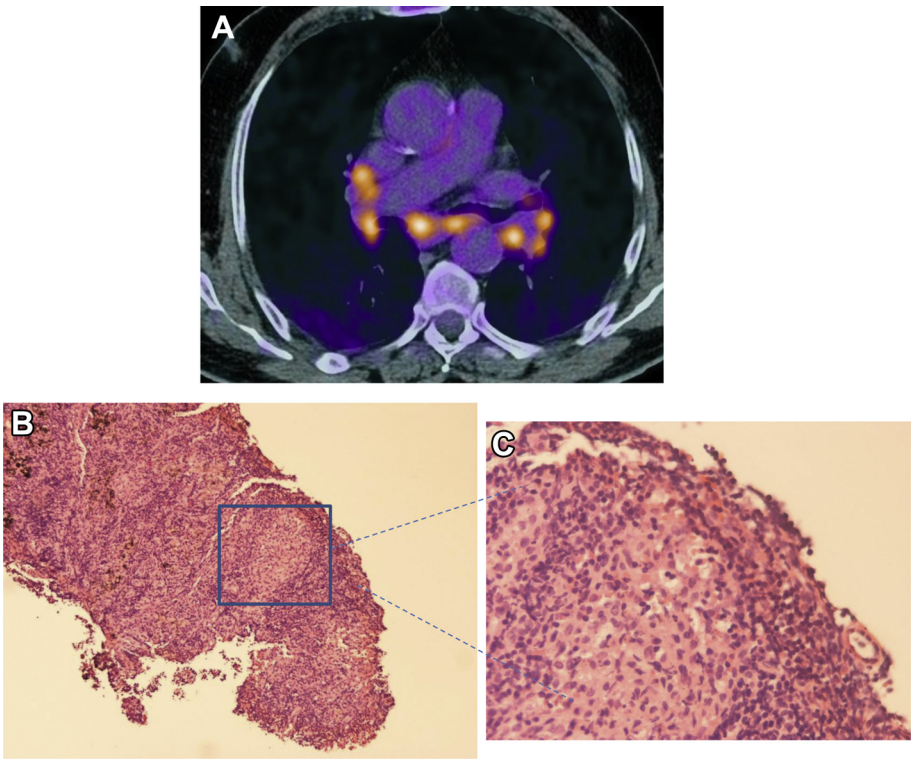

Figure 1 – *A-C, A 55-year-old man received pembrolizumab for metastatic melanoma, 200 mg IV every 3 wk. Restaging after four doses of pembrolizumab revealed regression with a near-complete response at most tumor locations with fludeoxyglucose positron emission tomography/CT imaging. However, follow-up fludeoxyglucose positron emission tomography/CT imaging also showed new highly metabolic active enlarged mediastinal and bilateral hilar lymph nodes (A). Endobronchial ultrasound-guided biopsy revealed focal infiltration by noncaseating granulomas (40× magnification [B]; 400× magnification [C]). PET/CT imaging was repeated 4 mo later after pembrolizumab therapy had been completed and showed complete remission of the melanoma and disappearance of the elevated metabolic activity of the mediastinal/hilar lymph nodes. This case meets the criteria for a pembrolizumab-associated drug-induced sarcoidosis-like reaction.*

should not be considered a DISR. Figure 2 outlines our proposed diagnostic approach to establishing a DISR.

Drugs Associated With a Drug-Induced Sarcoid-Like Reaction

Immune Checkpoint Inhibitors

Immune checkpoints are inhibitory pathways that modulate immune system activation and suppress antitumor T-cell responses. Immune checkpoint inhibitors (ICIs) alleviate tumor-induced immunosuppression of T cells and thereby enhance antitumor immunity.[153] These ICIs are bioengineered monoclonal antibodies that block the immune checkpoint pathway at various points and include (1) ipilimumab, an antagonistic monoclonal antibody against cytotoxic T lymphocyte antigen-4 (CTLA-4); (2) nivolumab and pembrolizumab, antibodies neutralizing programmed death protein 1 (PD-1); and (3) atezolizumab and avelumab, antibodies to programmed death-ligand 1. These ICIs have been proven to be effective in treatment of various cancers such as advanced melanoma, non-small cell lung carcinoma, renal cell carcinoma, and Hodgkin's lymphoma.[154]

ICIs not only enhance antitumor activities, but also stimulate the immune system resulting in immune-related adverse events (irAEs) such as immune thrombocytopenia, Sjogren syndrome, rheumatoid arthritis, polymyalgia rheumatica, psoriatic arthritis, seronegative polyarthritis, and DISRs.[155,156] Analysis of a French registry of 908 patients treated with ICIs[26] reported that 2% (n = 21) developed irAEs. Sarcoidosis was reported in only 2 cases (0.2%), involving mediastinal lymph nodes in both cases and uveitis in one case.[156]

Several reports have noted an association between DSIRs and ICI use. The most common ICI associated with DISRs is ipilimumab; however, cases have been reported with nivolumab and pembrolizumab. The most common underlying malignancy associated with an ICI-induced DISR has been melanoma, which probably relates to the clinical indication for ICI use. ICI-related DISRs have also been reported in patients with Hodgkin's lymphoma, prostate cancer, and uterine

TABLE 2] Differential Diagnosis of Granulomatous Reaction

Categories	Diseases
Infection	Tuberculosis Atypical mycobacterial infection Cryptococcosis Aspergillosis Histoplasmosis Blastomycosis Coccidioidomycosis Pneumocystis jiroveci pneumonia Mycoplasma infection Brucellosis Toxoplasmosis Schistosomiasis Cytomegalovirus infection Infectious mononucleosis
Inflammatory diseases	Sarcoidosis Granulomatous polyangiitis Crohn's disease Hypersensitivity pneumonitis Granulomatous histiocytic necrotizing lymphadenitis Rheumatoid nodule Giant cell myocarditis Lymphocytic interstitial pneumonias Primary biliary cirrhosis Necrotizing sarcoid granulomatosis
Malignancy	Hodgkin's lymphoma Non-Hodgkin's lymphoma Sarcoidosis-like reaction of malignancy
Miscellaneous	DISR Pneumoconiosis (beryllium, titanium, and aluminum) Granulomatous lesions of unknown significance syndrome Reaction to foreign bodies Aspiration of foreign materials

DISR = drug-induced sarcoidosis-like reaction.

leiomyosarcoma. DISRs have developed from 3 weeks to almost 2 years after initiating ICI therapy; however, only one reported case occurred > 36 weeks after starting ICI treatment.[157] DISRs were diagnosed an average of 4.6 months after the initiation of an ICI. Slightly more than one-half of the patients who developed ICI-related DISRs required antisarcoidosis treatment (Table 3). There is no obvious ICI dose threshold for the development of ICI-related DISRs.

The lung and skin are the most common organs involved with ICI-related DISRs. Common pulmonary manifestations of ICI-related DISRs include thoracic lymphadenopathy, pulmonary nodules, pneumonitis, and, less commonly, pleural effusions.[16,158,159] Retrospective studies of irAEs in patients with metastatic melanoma undergoing anti-CTLA-4 antibody therapy found that thoracic lymphadenopathy was detected in 5% to 6.7% of cases after a median time of 3 to 6 months from drug initiation.[158,159] However, pathology data were not reported in these analyses. It is not clear whether these thoracic lymphadenopathies associated with irAEs were reactive lymphadenopathy without granuloma formation or DISR-associated granulomatous lymphadenopathy.[155,156]

The skin is the second most common organ involved with a DISR from ICIs. Manifestations of cutaneous ICI-induced DISRs have included nodular intradermal lesions[18] and tattoo-associated granulomas.[1] Similar to sarcoidosis,[160] cutaneous DISRs are often recognized earlier than the detection of pulmonary involvement. Cutaneous DISRs need to be distinguished from other cutaneous irAEs related to ICIs that include lichenoid reactions, eczema, vitiligo, and pruritus. Rarely, ICIs are associated with serious cutaneous toxicities such as toxic epidermal necrolysis and a severe drug rash with eosinophila.[161] Other less commonly affected organs involved with ICI-induced DISRs include the spleen[16] and kidney.[162]

DISRs have rarely been reported with PD-1 and programmed death-ligand 1 checkpoint inhibitors. Nivolumab-induced DISRs have been reported in four cases to date involving thoracic lymph nodes, the parotid gland, and skin (Table 1). Pembrolizumab has been reported to induce DISRs involving the lung, lymph nodes, skin, eye, and bone (Table 1). Finally, a few cases of DISRs have been described in patients receiving a combination of checkpoint inhibitors (ipilimumab and nivolumab).[163]

Various mechanisms have been proposed to explain the development of DISRs in patients receiving ICIs. Ipilimumab may cause a DISR through anti-CTLA-4 monoclonal antibody inhibition of both cluster of differentiation (CD) 80 and CD86 on antigen-presenting cells; this inhibition could block T-cell signaling and prolong T-cell activation and restore T-cell proliferation. Although this T-cell-induced stimulation induced by ipilimumab enhances the patient's capacity to mount an antitumor immune response,[164,165] the resulting T-cell proliferation and increased expression of T-helper (Th) 1-associated markers[166,167] could potentially induce a DISR because these cells are abundant in active sarcoidosis and are thought to be integral to the development of sarcoid granuloma.[168] Ipilimumab also increases the number and function of Th17 cells that have been shown to promote granuloma formation and sarcoidosis-induced fibrosis.[169]

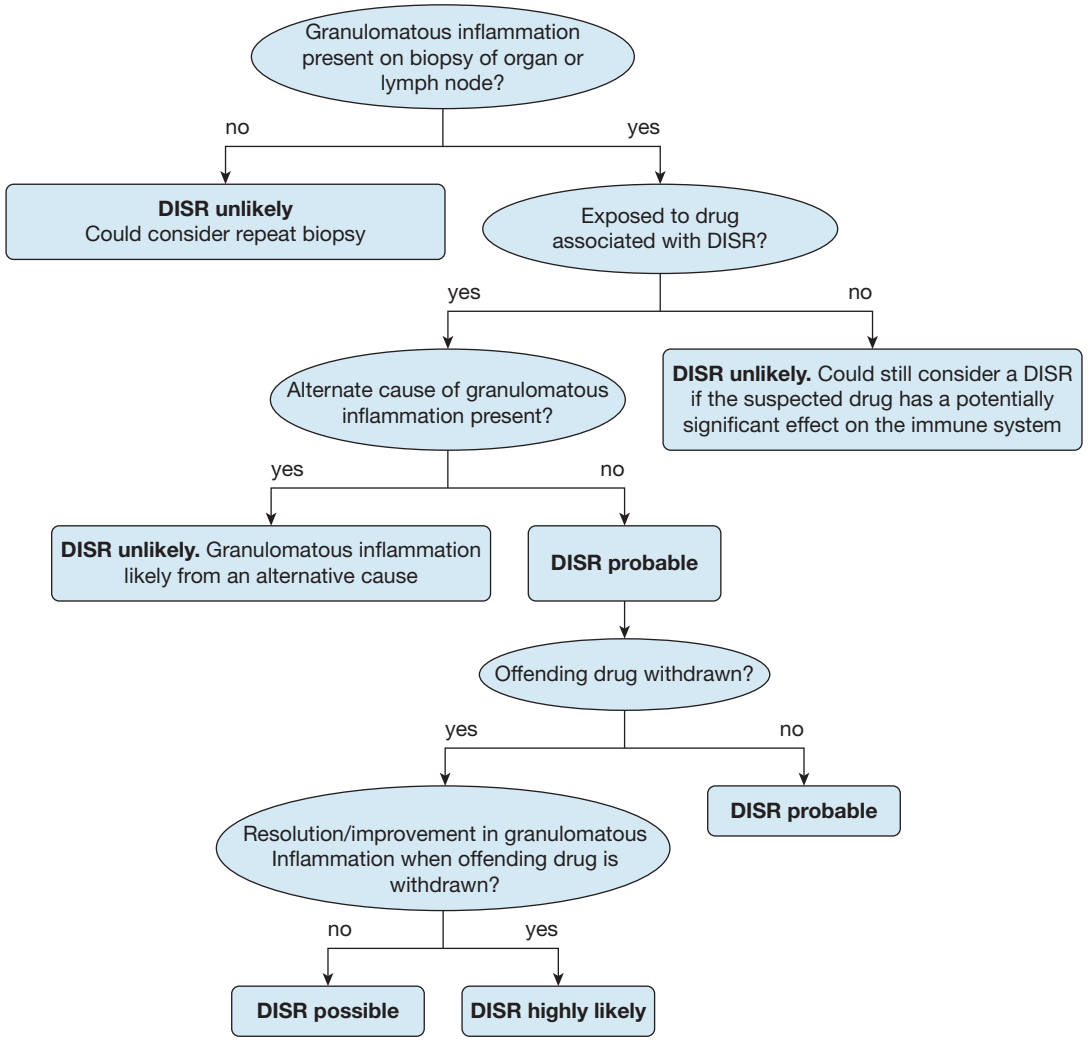

Figure 2 – *A proposed diagnostic approach to establishing a DISR. DISR = drug-induced sarcoidosis-like reaction.*

It is problematic to explain how PD-1 inhibitors such as nivolumab and pembrolizumab may cause a DISR. Recently, the PD-1 pathway was found to be upregulated in active sarcoidosis, with increased PD-1 expression demonstrated on CD4+ T cells and lymphoid areas surrounding granulomas.[170] Braun et al[170] found that downregulation of PD-1 expression on CD4+ T cells was associated with spontaneous resolution of sarcoidosis. Based on these data, it would appear paradoxical that an anti-PD-1 ICI antibody could cause

TABLE 3] Summary of Various Drugs Implicated in DISR

	Time From Drug Initiation to the Diagnosis of DISR (mo)		Requiring Antisarcoidosis Prescription (%)		Outcome Resolution (%)[a]	
Drug Class	No. of Patients	Mean (range)	%	No. of Patients	%	No. of Patients
ICIs	23	4.6 (0.7-21.2)	57.2	21	62	21
HAART	22	19.8 (3-48)	41.1	17	64.2	9
IFN	99	9.6 (1.5-120)	42.9	98	75.5	94
TNF-α antagonist	82	24.2 (1-84)	59.5	79	84.3	77

HAART = highly active antiretroviral therapy; ICI = immune checkpoint inhibitor; IFN = interferon; TNF = tumor necrosis factor. See Table 2 legend for expansion of other abbreviation.

[a]These are resolution estimates by the authors after reviewing these cases because the definitions of resolution were not consistent and/or clearly stated in many of these reports.

a DISR. However, similar to CTLA-4 inhibitors, anti-PD-1 ICIs can increase the number and function of Th17 cells and possibly cause a DISR on that basis.[13,171,172] Alternatively, these drugs may induce a DISR by causing a granulomatous immune reconstitution reaction to melanoma antigens.[173]

Because ICIs are used for the treatment of malignancies, it is important to recognize that a DISR can mimic a malignancy in terms of roentgenographic and PET scan findings. Therefore, the clinician should not presume that new or growing masses and/or lymph node enlargement represent spread of malignancy without further investigation. In addition, ICIs are associated with interstitial pneumonias such as organizing pneumonia, hypersensitivity pneumonitis, nonspecific interstitial pneumonia, and inflammatory bronchiolitis.[174] Therefore, these entities must be differentiated from ICI-induced DISRs.

ICI-induced irAEs often cause no symptoms or minimal symptoms and may resolve spontaneously or with withdrawal of the ICI. Furthermore, there is evidence that development of an irAE during ICI therapy for melanoma correlates with a potent antitumor response, possibly because an irAE may be a surrogate of an effective granulomatous antimelanoma response from cross-reaction with melanoma antigens. These data suggest that an ICI-related irAE, including a DISR, is a biomarker of an active antitumor effect of the ICI, and this would be a disincentive to discontinue ICI therapy.

Tumor Necrosis Factor-α Antagonists

Tumor necrosis factor (TNF)-α plays an important role in formation and maintenance of sarcoid granuloma.[175] Therefore, it is rational to consider TNF-α antagonists for the treatment of sarcoidosis. Interestingly, despite the data supporting the use of TNF-α antagonists for sarcoidosis treatment, paradoxically, TNF-α antagonist-induced DISRs have been described. TNF-α antagonist-induced DISRs appear most commonly with etanercept, but they may occur with any TNF-α antagonist (Table 1). TNF-α-associated DISRs occurred an average of 24 months after drug initiation. Sixty percent of patients with TNF-α-associated DISRs required antisarcoidosis treatment (Table 3).

A retrospective analysis from France showed that 10 out 28,000 (0.04%) patients developed sarcoidosis after treatment with TNF-α antagonists, which was higher than the regional prevalence of sarcoidosis of 6 per 100,000 per year.[15] Daien et al[15] reported 10 cases of TNF-α antagonist-induced DISRs. The median delay between TNF-α antagonist introduction and the development of a DISR was 18 months (range, 1-51). The most common organs involved were the lung (8/10, 80%) and skin (4/10, 40%). Radiographic presentations were typical of sarcoidosis, with mediastinal adenopathy and/or diffuse lung opacities. TNF-α antagonists were discontinued in nine cases, and improvement was observed in all of them. Corticosteroids were used in only 20% (2/10) of cases. The median delay between drug discontinuation and remission was 6 months for both clinical signs (range, 1-11 months) and radiographic findings (range, 2-12 months). In four cases, a different TNF-α antagonist was reintroduced after resolution of a DISR, and only one of these four patients had DISR recurrence that required steroid administration and discontinuation of the drug.

The exact mechanisms involved in TNF-α antagonist-induced DISRs are not clear. It is likely that TNF-α simultaneously stimulates and suppresses numerous cell signaling pathways depending on the surrounding inflammatory mileau.[15,140] Specific mechanisms that have been proposed include an imbalance in cytokine production, antibodies to TNF-α soluble receptor, an unopposed type I interferon (IFN) production promoting a shift toward a Th1/Th2 profile,[139] and neutralization of soluble TNF-α that could permit the activation of specific autoreactive T cells.[115]

IFN

IFNs are a group of cytokines that have been widely used in the treatment of various chronic disorders and cancers. IFN-alpha is produced by leukocytes, specifically by macrophages and dendritic cells. IFN-beta is produced by fibroblasts. The third form of IFN is IFN-gamma, which is produced by T-cell lymphocytes.[176,177] IFN-alpha has been widely used for the treatment of chronic hepatitis B virus and hepatitis C infection and various cancers such as chronic leukemia, malignant melanoma, and renal cell carcinoma. IFN-beta has been used extensively for the treatment of multiple sclerosis, whereas IFN-gamma has very limited clinical usage.[176] DISRs are more commonly associated with IFN-alpha than IFN-beta. No case of an IFN-gamma-induced DISR has been reported.

Currently, 99 cases have been published in the English literature describing the occurrence of sarcoidosis after IFN-alpha therapy (Table 1). IFN-alpha was most commonly used for the treatment of hepatitis C and chronic leukemia.[6] Lung and mediastinal lymph nodes

(70%) and skin (60%) were the most commonly reported organs involved with DISRs from IFN-alpha therapy.[6,45,77] IFN-alpha-induced DISRs have been detected from 6 to 104 weeks after the beginning of therapy, and in many cases, a cutaneous lesion was the first organ manifestation.[6] Although IFN-induced DISRs typically spontaneously regress with discontinuation of IFN therapy, cases have been described of IFN-induced DISRs that have resolved despite continuation of IFN therapy. This suggests that IFN may trigger a DISR but have no significant role in its maintenance. Rarely, systemic corticosteroids may be required in severe cases of infliximab-induced DISRs.

As mentioned, IFN-beta is rarely associated with DISRs, with only nine cases having been reported (Table 1). The diagnosis of these DISRs was made between 5 months and 10 years after initiation of IFN-beta therapy (Table 3). These DISRs most commonly involved the lung. In all cases, IFN therapy was discontinued and the DISR was resolved. Similar to ICIs, IFNs are associated with various interstitial pneumonias.[178] Therefore, the development of diffuse lung opacities in patients receiving IFNs warrants a thorough evaluation.

The exact pathogenesis of an IFN-induced DISR is not presently understood. Increased production of IFN-alpha has been linked to Th1 polarization and Th2 inactivation with an increased level of granuloma-promoting cytokines such as IL-2, IL-8, IL-12, IL-18, and IFN-gamma.[177,179,180] The relatively greater occurrence of DISRs with IFN-alpha therapy may be a reflection of a strong association between the allele 2 polymorphism in the IFN-alpha gene (*IFNA17*) and susceptibility to sarcoidosis[181]; notably, no significant association has been observed with the IFN-beta gene.[181] Further support for an association between IFN-alpha and sarcoidosis was demonstrated in a large European American cohort, where serum IFN-alpha activity was higher in sarcoidosis cases compared with matched control subjects; in addition, patients with sarcoidosis with extrapulmonary disease had higher serum IFN-alpha levels than those with isolated pulmonary sarcoidosis.[182]

Antiretroviral Therapy

Antiretroviral therapy (ART)-induced DISRs are immune reconstitution inflammatory syndrome reactions that occur in patients with HIV infection. ART increases the number and function of CD4 cells, and this may lead to induction of a granulomatous response to specific antigens resulting in a DISR (Table 1). ART may also exacerbate sarcoidosis in individuals who had concomitant HIV infection and sarcoidosis prior to initiating ART.[183,184] ART-induced DISRs develop an average of 20 months after starting ART, and only 40% of these patients require antisarcoidosis treatment (Table 3).

ART-induced DISR has only been demonstrated to occur when the CD4 count has risen from previous values and has exceeded 150 cells/mm^3.[31,37,183,185] The fact that DISRs have been reported with various ART regimens supports the premise that these reactions are most likely related to immune reconstitution rather than a specific drug effect.[31] As with other DISRs, those related to ART are indistinguishable from sarcoidosis. ART-induced DISRs most commonly involve the lungs, but they may occur in any organ including the liver, spleen, skin, parotid glands, salivary glands, peripheral lymph nodes, and muscle.[30] The most common presenting symptoms include dyspnea and cough; however, patients may be asymptomatic with the DISR detected by the presence of a chest radiographic abnormality.[36,185] Chest radiographs typically reveal bilateral interstitial infiltrates with or without hilar lymphadenopathy. The diagnosis of an ART-induced DISR requires a rigorous exclusion of granulomatous infections, such as mycobacterial and fungal infections, that are common in individuals with HIV infection. The presence of noncaseating granulomas does not exclude tuberculosis infection because this histology is seen in 20% of such cases.[186]

ART should not be discontinued when a DISR develops because corticosteroid therapy is routinely effective. Most initial corticosteroid dosing regimens have been with at least 20 mg of daily prednisone equivalent.[31,37,185] Asymptomatic cases do not require treatment because sarcoidosis immune reconstitution inflammatory syndrome may never cause symptomatic disease and may resolve without antigranulomatous therapy.[31]

Miscellaneous Drugs

There are few other drugs associated with granulomatous reactions in various organs similar to a DISR. Targeted *BRAF* inhibitors such as vemurafenib and dabrafenib are highly effective chemotherapy agents for metastatic melanoma associated with *BRAF* (B-Raf) V600E mutation. In isolated reports, *BRAF* inhibitors have been reported to cause a granulomatous reaction involving skin, liver, and kidney, but not lung (Table 4).[187-192]

TABLE 4] Drugs Associated With Granulomatous Reaction but Not Drug-Induced Sarcoidosis-Like Reaction

Drugs	No. of Cases	References
Nitrofurantoin	3	187-189
Etretinate	1	190
Thalidomide	1	191
Quetiapine	1	192

Nitrofurantoin has been reported to cause granulomatous reaction in single organs such as lung, kidney, and liver (Table 4). Additional drugs, including etretinate, thalidomide, and quetiapine, have been reported to cause a granulomatous reaction involving a single organ, such as skin and liver, in isolated reports (Table 4). Because these drugs have been associated with granulomatous inflammation in one organ without any other obvious systemic effects, they have not been demonstrated to cause systemic granulomatous syndromes and therefore fail to meet criteria for a DISR.

Implant- and Device-Induced Sarcoid-Like Reactions

Sarcoidosis-like reactions may also be a manifestation of an autoimmune inflammatory syndrome induced by adjuvants (ASIA),[193,194] which was previously termed human adjuvant disease. ASIAs occur by adjuvants chronically stimulating their effect on the immune pathway and preventing antigens from being degraded, therefore prolonging antigen exposure to antigen-presenting cells.[193] The adjuvants associated with ASIAs include silicone,[195] hyaluronic acid,[196] and mineral oil.[197] Several sarcoidosis-like reactions related to ASIAs have been reported after silicone breast implantation,[198-201] with resolution of the sarcoidosis-like reaction after removal of the implant.[202] Multisystem granulomatous reactions related to ASIAs should be differentiated from local foreign body granulomatous reactions (eg, siliconomas).[203]

Sarcoidosis-like reactions have been reported in two cases after hip replacement.[204,205] Both cases were associated with systemic dissemination of prosthetic particles that were found in distant organs. These findings were suggestive of a granulomatous response to the hip prosthetic particles from wear and tear of the prosthesis. Multiple organ granulomas were found in both cases including in the lung, liver, spleen, eye, and visceral lymph nodes. Although these sarcoidosis-like reactions may relate to foreign body granulomas from disseminated particles, erythema nodosum was reported in one of the cases, suggesting that systemic sarcoidosis-like systemic reaction did occur, which may have been a form of ASIA. These granulomatous reactions occurred 6 months after hip arthroplasty.[204] In both cases, the granulomas resolved after removal of prosthetic device and treatment with corticosteroids. Two additional reports of a localized foreign body granulomatous reaction of synovium after knee replacement surgery have been reported.[206,207] However, there was no evidence that a systemic granulomatous response was present in either case.

DISR Treatment Recommendations

As described, DISRs commonly resolve spontaneously or with withdrawal of the offending agent. DISRs may present with minimal or even no symptoms at all. For these reasons, the clinician should weigh the benefit of continuing the offending drug with the severity of the DISR. If the drug is of significant benefit and the effects of the DISR are minimal, the drug may be continued. If the offending drug has been beneficial but the DISR is causing significant symptoms, then corticosteroids or other antisarcoidosis therapies could be considered. In case of ICI-induced DISRs, the presence of an irAE may be associated with a potent antitumor response and would therefore be an incentive to continue ICI therapy. In some instances, switching to another drug in the same class as the offending agent may result in resolution of the DISR. As previously mentioned, this could be considered in the case of TNF-α antagonist-induced DISRs, as in one report, three of four patients who were switched to a different TNF-α antagonist did not have recurrence of a DISR.[15] We would expect that switching ART agents would not prevent the recurrence of a DISR because this seems to be a class effect related to immune reconstitution.

When corticosteroids or other antisarcoidosis agents are required for the treatment of a DISR, we suspect that similar doses may be used as for sarcoidosis. There are inadequate data to recommend a specific dosing regimen for DISRs. As mentioned, usually an initial dose of at least 20 mg of daily prednisone equivalent has been used. The dose of corticosteroid and other immunosuppressants may be modified based on the patient's underlying condition. For example, because patients with HIV infection are at a high risk of developing an opportunistic infection, it would be prudent to treat an ART-induced DISR with a relatively low dose of corticosteroids.

Implications of DISRs in Terms of Our Understanding of Sarcoidosis

The exact immunopathogenesis of sarcoidosis is currently unknown, and the diagnosis of sarcoidosis currently requires the subjective criteria of a clinical presentation consistent with sarcoidosis.[208] Because of these two facts, it is unclear whether DISRs are inducing a syndrome very similar to sarcoidosis or are truly causing sarcoidosis. Given that the clinical manifestations of DISRs are essentially identical to those seen with sarcoidosis, we suspect that the immunopathogenesis of DISRs is close to or identical to that of sarcoidosis. Just as extrapolation of our understanding of mechanisms causing chronic beryllium disease, a condition that is radiographically and pathologically similar to sarcoidosis,[209] emphasized the importance of an interplay between the human leukocyte antigen class II molecule, antigen, and T-cell receptor in the development of sarcoidosis,[210,211] so too may our comprehension of the mechanisms causing DISRs accelerate our knowledge of how sarcoidosis develops. The aforementioned proposed mechanisms for the various drugs associated with DISRs suggest that several mechanisms may be important in the development of sarcoidosis, including stimulation of a host T-cell-induced antitumor immune response via prolonging T-cell activation, increased expression of Th1-associated markers, upregulation of IFN-alpha, and an increase in CD4 cells. Although most of these mechanisms have previously been implicated as important in the development of sarcoidosis, detailed analyses of the mechanisms causing DISRs are likely to incrementally increase our understanding of the mechanisms causing sarcoidosis.

Summary

DISRs are drug-induced sarcoidosis syndromes that are indistinguishable from sarcoidosis, except that they uniformly resolve with discontinuation of the offending agent. Clinicians should be aware of this entity because it may be misdiagnosed resulting in unnecessary testing and/or therapy. Similar to sarcoidosis, treatment of a DISR is not mandated because it may never cause symptoms, quality of life impairment, or organ dysfunction. It appears that when treatment of a DISR is required, standard antisarcoidosis drugs and doses are effective. The offending drug need not be discontinued because in some situations the development of a DISR may suggest a beneficial effect of the induced drug. Drugs that cause DISRs may provide insight into the immunopathogenesis of sarcoidosis.

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