Clinicopathologic Features of Tissue Granulomas in Transplant Recipients

A Single Center Study in a Nontuberculosis Endemic Region

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Context.—There is a paucity of literature about tissue granulomas in transplant patients.

Objective.—To characterize the clinicopathologic features of granulomas in this population and develop a clinically judicious approach to their evaluation.

Design.—We performed chart reviews of solid organ and allogeneic hematopoietic stem cell transplant recipients at Yale New Haven Hospital to identify patients with granulomas on biopsy obtained pathologic specimens. Pretransplant and posttransplant specimens were included. Data points included demographics, clinical presentation, epidemiologic risk factors, biopsy indication, location and timing, immunosuppression, histopathology, microbiology, and associated clinical diagnosis. Granuloma-related readmissions and mortality were recorded at 1, 3, and 12 months.

Results.—Biopsy proven granulomas were identified in 56 of 2139 (2.6%) patients. Of 56, 16 (29%) were infectious. Common infectious etiologies were bartonellosis (n = 3) and cytomegalovirus hepatitis (n = 3). Tuberculosis was not identified. Clinical symptoms prompted tissue biopsy in 27 of 56 (48.2%) cases while biopsies were obtained for evaluation of incidental findings or routine disease surveillance in 29 of 56 (51.8%). Presence of symptoms was significantly associated with infectious etiologies; 11 of 27 (40.7%) symptomatic patients compared with 5 of 29 (17.2%) asymptomatic patients had infectious causes. One death from granulomatous cryptogenic organizing pneumonia occurred. In pretransplant asymptomatic patients, no episodes of symptomatic disease occurred posttransplantation.

Conclusions.—Granulomas were uncommon in a large transplant population; most were noninfectious but presence of symptoms was associated with infectious etiologies. Granulomas discovered pretransplant without clear infectious etiology likely do not require prolonged surveillance after transplantation. Symptomatology and epidemiologic risk factors should guide extent of microbiologic evaluation.

Granulomas are clusters of epithelioid histiocytes, often characterized by irregular contours and an abundance of eosinophilic cytoplasm, which may coalesce into multinucleated giant cells and form as an inflammatory response to a variety of infectious and noninfectious conditions.1–3 While granulomatous diseases have been well studied in the general population, there is insufficient literature on the clinical significance of granulomas in hematopoietic stem cell transplant recipients (HSCTR) and solid organ transplant recipients (SOTR), populations that are particularly vulnerable to infection. Moreover, the prevalence and etiologies of granulomatous diseases in this population are largely unknown.

Common granuloma sites include the lung, liver, lymph node, skin, bone marrow, kidney, and bowel,1–4 among others with prevalence varying by location. Pulmonary and hepatic granulomas are the best characterized, with reported incidences ranging from 10% to 15% and 2% to 10%, respectively, in the general population5–8 (Table 1).

Tuberculosis is the most common infectious cause of granulomas worldwide,2,3 though a myriad of other bacterial, fungal, viral, and parasitic infectious agents are known causes of granulomatous disease (Table 1). In the United States, mycobacterial infections, both tuberculous and nontuberculous, and endemic fungi are the most common infectious etiologies,3,5–11 though much of these data are gleaned exclusively from pulmonary granulomas. Common noninfectious etiologies include autoimmune conditions, particularly sarcoidosis, as well as neoplastic and allergic conditions4 (Table 1). Notably, an underlying etiology often remains undefined. In a study of 500 lung granulomas, 42% were without an identifiable etiology.9

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Similarly, hepatic granulomas are without a known cause in 10% to 36% and bone marrow granulomas in up to 64%. There are unique considerations in the transplant setting that make the approach to the differential diagnosis for granulomatous disease more challenging. Graft-versus-host disease, posttransplant lymphoproliferative disease, and cord colitis syndrome have all been associated with tissue granulomas in transplant patients. There is also risk of drug-induced renal, pulmonary, and hepatic granulomatous inflammation from immunosuppressive therapy and prophylactic antimicrobial agents. Existing literature does not suggest that renal transplant rejection is typically associated with granuloma formation; however, there are reports of granulomatous inflammation in hepatic transplant rejection.

| Location     | Estimated Prevalence | Common Infectious Etiologies | Common Noninfectious Etiologies |
|--------------|----------------------|------------------------------|-------------------------------|
| Pulmonary    | 10%–15%⁴             | MTB                          | Sarcoïdosis                    |
|              |                      | NTM                          |                               |
|              |                      | Brucella spp.                |                               |
|              |                      | Coccidioides spp.            |                               |
|              |                      | Cryptococcus spp.            |                               |
|              |                      | Histoplasma capsulatum       |                               |
|              |                      | Blastomyces spp.             |                               |
| Hepatic      | 2%–10%⁶             | MTB                          | Sarcoïdosis                    |
|              |                      | NTM                          |                               |
|              |                      | Bartonella henselae          |                               |
|              |                      | Brucella spp.                |                               |
|              |                      | Coxiella burnetii            |                               |
|              |                      | Coccidioides spp.            |                               |
|              |                      | Cryptococcus spp.            |                               |
|              |                      | Histoplasma capsulatum       |                               |
| Skin         | 1%–7%²²,²³           | MTB                          | Sarcoïdosis                    |
|              |                      | NTM                          |                               |
|              |                      | Mycobacterium leprae         |                               |
|              |                      | Actinomyces spp.             |                               |
|              |                      | Bartonella henselae          |                               |
|              |                      | Chlamydia trachomatis* (LGV) |                               |
|              |                      | Treponema pallidum           |                               |
|              |                      | Blastomyces spp.             |                               |
|              |                      | Coccidioides spp.            |                               |
|              |                      | Cryptococcus spp.            |                               |
|              |                      | Histoplasma capsulatum       |                               |
| Lymphatic    | 8%–25%²⁴–²⁶          | MTB                          | Sarcoïdosis                    |
|              |                      | NTM                          |                               |
|              |                      | Bartonella spp.              |                               |
|              |                      | Francisella tularensis       |                               |
|              |                      | Chlamydia trachomatis* (LGV) |                               |
|              |                      | Treponema pallidum           |                               |
|              |                      | Blastomyces spp.             |                               |
|              |                      | Coccidioides spp.            |                               |
|              |                      | Cryptococcus spp.            |                               |
|              |                      | Histoplasma capsulatum       |                               |
| Kidney       | <1%²⁷               | Bartonella henselae          | Drug-induced interstitial nephritis |
|              |                      | Brucella spp.                | Sarcoïdosis                    |
|              |                      | MTB                          |                               |
|              |                      | NTM                          | Sarcoïdosis                    |
|              |                      | Enterobacteriaceae (XPN)     |                               |
| Bone marrow  | 1%–1.5%⁴,²⁸         | MTB                          | Sarcoïdosis                    |
|              |                      | NTM                          |                               |
|              |                      | Brucella spp.                | Sarcoïdosis                    |
|              |                      | Histoplasma capsulatum       |                               |
| Bowel        | 21%–60% of Crohn disease patients⁹¹ | Uncommonly reported | Crohn disease |

Abbreviations: CMV, cytomegalovirus; DILI, drug-induced liver injury; EBV, Epstein-Barr virus; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; LGV, lymphogranuloma venereum; MTB, Mycobacterium tuberculosis; NTM, nontuberculous mycobacteria; PBC, primary biliary cholangitis; XPN, xanthogranulomatous pyelonephritis.

a Serovars L1, L2, and L3 as observed in lymphogranuloma venereum.
Increased immunosuppression in transplant recipients broadens the differential diagnosis for infectious etiologies of granulomatous disease and may increase the risk for disseminated infection. Current literature regarding infectious causes of granulomas in transplant recipients is extremely sparse and mostly limited to case reports and small case series. Adenovirus, BK polyomavirus, Mycobacterium tuberculosis (MTB), Candida albicans, Cryptococcus neoformans, and Histoplasma capsulatum have been implicated as causes of granulomatous interstitial nephritis in reports of renal allograft recipients.15,16,18 Bartonella henselae has been reported as a cause of granulomatous disease, predominantly in renal transplant patients but also in hepatic transplant recipients.19 Posttransplant hepatic granulomas have also been associated with cytomegalovirus (CMV), hepatitis B, hepatitis C, and tuberculosis.17,20 An additional consideration is that granulomas discovered before transplantation, particularly if infectious in etiology, may evolve after transplantation when recipients are exposed to highly immunosuppressive therapies for prolonged periods. Indeed, a recent study of lung transplant patients identified as part of routine disease surveillance in asymptomatic patients. Further data were obtained on patient characteristics, immunosuppression regimen at time of granuloma discovery, change in immunosuppression after granuloma discovery, time from transplantation to granuloma discovery, histopathology, and microbiologic diagnostics including Mycobacterium tuberculosis polymerase chain reaction (MTB PCR) and interferon gamma release assay. Charts were also reviewed for presence of epidemiologic MTB risk factors, including country of birth, history of international travel, human immunodeficiency virus (HIV) seropositivity, and history of homelessness or incarceration. The final clinical diagnosis for each case was determined based on available microbiologic, histopathologic, and laboratory data as well as clinical determination of the treatment teams. A limited, independent slide review was also performed by the authors. We recorded hospital readmissions and mortality due to granuloma-related disease at 1, 3, and 12 months after granuloma diagnosis for those discovered posttransplant. Patients who had granulomas discovered before transplantation were followed for 1 year posttransplant.

Statistical Analysis

We used statistical tests to identify factors associated with the presence of infectious granulomas. X² or Fisher's exact test was used for categoric variables, and independent samples t-test was used for continuous variables. All tests were 2-tailed with significance at P < .05. JMP Pro 15.0.0 software (SAS Institute, Cary, North Carolina) was used for all data analysis.

RESULTS

Our chart review revealed 2139 transplant recipients of whom 487 (22.8%) were HSCTR and 1652 (77.2%) were SOTR. Among the 1652 SOTR, 1062 (64.3%) were kidney transplant recipients, 486 (29.4%) were liver transplant recipients, and 104 (6.3%) were heart transplant recipients. Granulomas were identified in 56 (2.6%) of 2139 total patients. The average age of patients with granulomas was 53.4 years (range, 13–73), 29 of 56 (51.8%) patients were male, and 42 of 56 (75%) were white.

Of 56 total granulomas, 18 (32.1%) were found in HSCTR, whereas 38 (67.9%) were found in SOTR (Table 2). The overall prevalence of granulomas in HSCTR was 3.7% (18 of 487) compared with 2.3% (38 of 1652) in SOTR. Of 38 granulomas identified in SOTR, 26 (68.4%) were identified in liver transplant recipients (5.4% [26 of 486] of all liver transplant recipients), 11 (28.9%) were identified in kidney transplant recipients (1% [11 of 1062] of all kidney transplant recipients) and 1 (2.6%) was identified in a heart transplant recipient (1% [1 of 104] of all heart transplant recipients). Fourteen (25%) of the 56 total granulomas were identified on pathology specimens obtained before organ transplant and 42 (75.0%) were identified after transplantation. Among granulomas found posttransplant, the median time between transplant and granuloma discovery was 1.57 years (range, 0.15–25.7). The most common locations of the 56 total granulomas were the liver (n = 18, 32.1%), lung (n = 14, 25.0%), skin (n = 8, 14.2%), and lymph node (n = 5, 8.9%), although granulomas were also infrequently identified on biopsies from bone marrow, colon, nasal cavity, small bowel, finger, paraspinal muscle, kidney, and spleen. There were no substantial histopathologic differences observed in infectious compared with noninfectious etiologies. Specifically, the vast majority of granulomas (n = 51, 91.1%) were nonnecrotizing. Of 5 necrotizing granulomas, 3 were of an infectious etiology and 2 were noninfectious.

Symptoms prompted biopsy in 27 of 56 (48.2%) patients, whereas in the remaining 29 cases (51.8%) biopsies were obtained for further evaluation of incidentally discovered granulomas in transplant recipients. We identified patients with granulomas discovered before transplantation, particularly if infectious in etiology, may evolve after transplantation when recipients are exposed to highly immunosuppressive therapies for prolonged periods. Indeed, a recent study of lung transplant patients discovered granulomas associated with increased risk of mycobacterial infection postransplantation.6
in 9 patients (33.3%), upper respiratory tract symptoms in 4 patients (14.8%), and dermatologic symptoms in 5 patients (18.5%). Of 56 total granulomas, 16 (28.6%) were determined to be infectious in etiology (Table 3, Figure 1). Of the 16 infectious granulomas, 12 were found in SOTR (31.6% of all 38 SOTR granulomas) and 4 were found in HSCTR (22.2% of all 18 HSCTR granulomas). Eleven of 16 (68.8%) were found in symptomatic patients, and 5 of 16 (31.2%) in asymptomatic patients (Figure 1). On univariate analysis, infectious granulomas were significantly associated with the presence of symptoms (40.7% [11 of 27] of symptomatic patients versus 17.2% [5 of 29] of asymptomatic patients, \( P = .05 \)) and diagnosis in the posttransplant setting (7.1% [1 of 14] of pretransplant diagnoses versus 35.7% [15 of 42] of posttransplant diagnoses, \( P = .05 \)).

The most common infectious etiologies among the 16 infectious cases included bartonellosis (n = 3; 18.8%), CMV (n = 3; 18.8%), cryptococcosis (n = 2; 12.5%), and bacterial skin and soft tissue infection (n = 2; 12.5%). Bartonellosis was diagnosed via a combination of diagnostic techniques as well as expert opinion of consulting infectious disease physicians. In 2 cases, bartonellosis was diagnosed via positive Bartonella PCR on tissue as well as positive serologies, and in 1 of these cases, positive coccobacilli seen on Warthin Starry stain. In the third case, the diagnosis was made via a greater than 4-fold rise in Bartonella IgG titers from acute to convalescent serum, known exposure to cats, compatible clinical syndrome with improvement on antibiotic treatment, and expert opinion of consulting infectious disease specialists (Figure 2, A). CMV hepatitis was diagnosed in 2 cases via positive CMV tissue immunostaining in conjunction with high-grade CMV viremia (Figure 2, B and C). In the third case, CMV hepatitis was diagnosed based on a combination of markedly elevated CMV plasma viral load, compatible clinical syndrome, including elevated transaminases and pancytopenia with atypical lymphocytosis, complete normalization of serum transaminase levels after treatment with valganciclovir, and expert opinion of consulting infectious disease physicians. This patient was also notably high risk for CMV disease being a CMV donor positive, recipient negative liver transplant recipient who was less than 1 year from transplant and not on prophylactic antiviral agents. Histopathology was nonspecific in this case and revealed a patchy mononuclear infiltrate with mild lobular hepatitis and no significant endothelitis or hepatic steatosis. Cryptococcal infections were diagnosed via a positive tissue culture in 1 case and a positive Grocott methenamine-silver stain and mucicarmine stain in the other case (Figure 2, D through F). Bacterial skin and soft tissue infections were diagnosed via positive bacterial tissue cultures.

The most common biopsy sites for infectious granulomas were lung (n = 6), liver (n = 5), and skin (n = 3) (Table 2, Figure 1). MTB PCR was ordered in 5 of 56 cases (8.9%) in tissue specimens obtained from liver (n = 2), colon (n = 1), lymph node (n = 1), and muscle (n = 1). Three of these were ordered on specimens from symptomatic patients. All 5 were negative. No patients in this cohort had documented MTB epidemiologic risk factors or positive interferon gamma release assay.

### Table 2. Summary of Study Population and Identified Tissue Granulomas

| Study Population                          | No. (%) |
|------------------------------------------|---------|
| Total number of patients examined        | 2139    |
| HSCTR                                    | 487 (22.8) |
| SOTR                                     | 1652 (77.2) |
| Liver                                    | 486 (29.4) |
| Kidney                                   | 1062 (64.3) |
| Heart                                    | 104 (6.3) |
| Identified granulomas                    | 56      |
| Total number of granulomas identified    | 56      |
| HSCTR                                    | 18 (32.1) |
| SOTR                                     | 38 (67.9) |
| Liver                                    | 26 (68.4) |
| Kidney                                   | 11 (28.9) |
| Heart                                    | 1 (2.6)  |
| Pretransplant versus Posttransplant      |         |
| Pretransplant                            | 14 (25) |
| Posttransplant                           | 42 (75) |
| Necrotizing versus Nonnecrotizing         |         |
| Necrotizing                              | 5 (8.9) |
| Nonnecrotizing                           | 51 (91.1) |
| Infectious versus Noninfectious          |         |
| SOTR                                     | 38      |
| Infectious                               | 12 (31.6) |
| Noninfectious                            | 26 (68.4) |
| HSCTR                                    | 18      |
| Infectious                               | 4 (22.2) |
| Noninfectious                            | 14 (77.8) |

| Symptomatic versus Asymptomatic          |         |
| Symptomatic                              | 27 (48.2) |
| Infectious                               | 11 (40.7) |
| Noninfectious                            | 16 (59.3) |
| Asymptomatic                             | 29 (51.8) |
| Infectious                               | 5 (17.2) |
| Noninfectious                            | 24 (82.7) |
| Biopsy site                              |         |
| Liver                                    | 18 (32.1) |
| Lung                                     | 14 (25.0) |
| Skin                                     | 8 (14.2) |
| Lymph node                               | 5 (8.9) |
| Bone marrow                              | 2 (3.6) |
| Colon                                    | 2 (3.6) |
| Nasal cavity                             | 2 (3.6) |
| Small bowel                              | 1 (1.8) |
| Finger                                   | 1 (1.8) |
| Paraspinal muscle                        | 1 (1.8) |
| Kidney                                   | 1 (1.8) |
| Spleen                                   | 1 (1.8) |

Abbreviations: HSCTR, hematopoietic stem cell transplant recipients; SOTR, solid organ transplant recipients.
inflammatory bowel disease (n = 3; 7.5%), and sirolimus-induced pneumonitis (n = 3; 7.5%). The etiologies of 12 of 40 (30%) were not established, but were presumed to be noninfectious based on a combination of lack of positive microbiologic studies, clinical assessment of treating physicians, lack of clinical symptoms, and clinical stability without antimicrobial therapy and/or with increases in immunosuppression. Microbiologic workup was limited in many of the cases without an established diagnosis and included bacterial tissue culture in 3 of 12 cases, fungal tissue culture in 1 case, and acid-fast tissue culture in 3 of 12 cases. An important distinction with other published reports is the absence of mycobacterial (MTB and non-tuberculous mycobacteria) and dimorphic fungal causes in our cohort. However, no patients had epidemiologic risk factors for MTB and the study was performed in a single center in a geographically nonendemic area. Patients with both infectious and noninfectious granulomas had favorable outcomes. The lack of hospital readmissions and low-associated mortality at 1-year postgranuloma discovery, even with subsequent increases in immunosuppression in many patients, suggests that infectious diagnoses were not frequently missed.

Our data have meaningful clinical implications regarding the approach to newly discovered tissue granulomas in HSCTR and SOTR. The identification of granulomas in patients who have undergone transplantation should not reflexively trigger a barrage of microbiologic testing. Rather, patients should be risk stratified according to the likelihood of having an infectious etiology. Based on our study findings, the most important characteristics in determining the extent of microbiologic evaluation are the presence of clinical symptoms and epidemiologic risk factors for MTB and endemic fungi. Asymptomatic patients from non-MTB and nondimorphic fungal endemic areas in whom granulomas are discovered incidentally are unlikely to have an infectious etiology and thus in those patients, microbiologic testing may mostly be limited to standard tissue cultures and stains. Interestingly, of 5 cases with infectious etiologies in asymptomatic patients, 2 were associated with cryptococcal infection and 2 with CMV hepatitis suggesting that testing for these 2 pathogens may be considered. MTB PCR does not need to be routinely applied to tissue specimens in these patients. In contrast, patients in whom granulomas are discovered as part of an evaluation of clinical symptoms are at significantly higher risk of having an infectious cause. A wide variety of causative pathogens including bacterial, fungal, and viral causes were evident in this study. Given the limited number of infectious granulomas identified, it is not possible to make precise recommendations for specific testing. However, bartonellosis may be a more common etiology in transplant recipients and should be considered, particularly in patients with fever and other systemic symptoms.

In addition, this study suggests that granulomas discovered incidentally in asymptomatic patients before transplantation are unlikely to become clinically significant associated with new-onset symptomatic disease after transplantation and with increased immunosuppression.

**DISCUSSION**

Tissue granulomas were uncommon in a large transplant population with an overall prevalence similar to that of the general population (Table 1). Though susceptible to a greater array of infectious and noninfectious processes associated with formation of granulomas, transplant recipients may be unable to mount a vigorous immune response critical for immune cell recruitment that leads to granuloma formation.21 The diminished immune response may also account for the paucity of necrotizing granulomas in this study, even with infectious causes.

The etiologies of infectious granulomas were generally consistent with findings from previously published literature among immunocompetent hosts, though bartonellosis was notably common in our cohort, and symptomatic with fever in all 3 cases. An important distinction with other published reports is the absence of mycobacterial (MTB and non-tuberculous mycobacteria) and dimorphic fungal causes in our cohort. However, no patients had epidemiologic risk factors for MTB and the study was performed in a single center in a geographically nonendemic area. Patients with both infectious and noninfectious granulomas had favorable outcomes. The lack of hospital readmissions and low-associated mortality at 1-year postgranuloma discovery, even with subsequent increases in immunosuppression in many patients, suggests that infectious diagnoses were not frequently missed.

Our data have meaningful clinical implications regarding the approach to newly discovered tissue granulomas in HSCTR and SOTR. The identification of granulomas in patients who have undergone transplantation should not reflexively trigger a barrage of microbiologic testing. Rather, patients should be risk stratified according to the likelihood of having an infectious etiology. Based on our study findings, the most important characteristics in determining the extent of microbiologic evaluation are the presence of clinical symptoms and epidemiologic risk factors for MTB and endemic fungi. Asymptomatic patients from non-MTB and nondimorphic fungal endemic areas in whom granulomas are discovered incidentally are unlikely to have an infectious etiology and thus in those patients, microbiologic testing may mostly be limited to standard tissue cultures and stains. Interestingly, of 5 cases with infectious etiologies in asymptomatic patients, 2 were associated with cryptococcal infection and 2 with CMV hepatitis suggesting that testing for these 2 pathogens may be considered. MTB PCR does not need to be routinely applied to tissue specimens in these patients. In contrast, patients in whom granulomas are discovered as part of an evaluation of clinical symptoms are at significantly higher risk of having an infectious cause. A wide variety of causative pathogens including bacterial, fungal, and viral causes were evident in this study. Given the limited number of infectious granulomas identified, it is not possible to make precise recommendations for specific testing. However, bartonellosis may be a more common etiology in transplant recipients and should be considered, particularly in patients with fever and other systemic symptoms.

In addition, this study suggests that granulomas discovered incidentally in asymptomatic patients before transplantation are unlikely to become clinically significant

| Table 3. Etiology of Infectious and Noninfectious Tissue Granulomas |
|---------------------------------------------------------------|
| **Etiology of Granuloma** | **No. (%)** |
| Infectious granulomas (n = 16) | |
| Bartonellosis | 3 (18.8) |
| CMV hepatitis | 3 (18.8) |
| Cryptococcal pneumonia | 2 (12.5) |
| Superinfected SSTI | 2 (12.5) |
| Pneumococcal pneumonia | 1 (6.3) |
| HMPV pneumonia | 1 (6.3) |
| *Stenotrophomonas pneumonia* | 1 (6.3) |
| Blastomyces skin infection | 1 (6.3) |
| PJP | 1 (6.3) |
| HCV cirrhosis | 1 (6.3) |
| Noninfectious granulomas (n = 40) | |
| Unknown—presumed noninfectious | 12 (30.0) |
| T cell–mediated rejection | 5 (12.5) |
| Inflammatory bowel disease | 3 (7.5) |
| Sirolimus-induced pneumonitis | 3 (7.5) |
| Sarcoïdosis | 2 (5.0) |
| Chronic sinusitis | 2 (5.0) |
| Ruptured cyst | 2 (5.0) |
| Primary biliary cirrhosis | 2 (5.0) |
| Infiltrative skin carcinoma | 2 (5.0) |
| Aspiration pneumonitis | 1 (2.5) |
| Cryptogenic organizing pneumonia | 1 (2.5) |
| Drug-induced liver injury | 1 (2.5) |
| T-cell lymphoma | 1 (2.5) |
| Autoimmune hepatitis | 1 (2.5) |
| Lung adenocarcinoma | 1 (2.5) |
| Acute interstitial nephritis | 1 (2.5) |

Abbreviations: CMV, cytomegalovirus; HCV, hepatitis C; HMPV, human metapneumovirus; PJP, *Pneumocystis jirovecii* pneumonia; SSTI, skin and soft tissue infection.
Figure 1. Flow diagram depicting granuloma location, clinical diagnosis, histopathology, and results of MTB PCR testing. Cases are grouped based on presence or absence of infectious etiology and clinical symptoms. Abbreviations: ACR, acute cellular rejection; AIN, acute interstitial nephritis; CMV, cytomegalovirus; COP, cryptogenic organizing pneumonia; DILI, drug-induced liver injury; HCV, hepatitis C virus; HMPV, human metapneumovirus; IBD, inflammatory bowel disease; MTB, Mycobacterium tuberculosis; PBC, primary biliary cholangitis; PCR, polymerase chain reaction; PJP, Pneumocystis jirovecii pneumonia; PNA, pneumonia; SSTI, skin and soft tissue infection.
posttransplant. No patients in this study in whom granulomas were discovered before transplantation, including those without a known diagnosis, experienced new onset-symptomatic disease attributable to the granulomatous process after transplantation and with increased immunosuppression at 1 year posttransplant. Absent symptoms or a clear infectious diagnosis, routine posttransplant surveillance of incidentally discovered pretransplant granulomas is unlikely to be necessary.

There are several notable limitations to this study. Our findings are not generalizable to regions with higher prevalence of MTB and endemic fungi. In addition, a final clinical diagnosis was unable to be obtained in 12 of 40 (30%) noninfectious cases. These granulomas were presumed to be noninfectious based on the clinical judgment of the treatment teams, as well as the favorable outcomes seen without use of antimicrobial agents and increases in immunosuppression. However, without a confirmed clinical diagnosis it is possible that some of these granulomas may have been miscategorized. Of these 12 cases, only 3 had tissue cultures sent for bacteria, 1 had tissue cultures sent for fungi, and no tissue cultures were sent for acid-fast bacilli. Fungal and acid-fast stains were performed on 4 of these specimens. Still, it should be noted that the inability to confirm a diagnosis is consistent with prior literature in immunocompetent hosts in which 10% to 64% of granulomas are without an identifiable etiology.4,7,9 Moreover, the positive outcomes among the patients in our study suggest that infections were not missed. In addition, it should be noted that 3 of 5 patients in whom liver allograft T-cell-mediated rejection was considered to be the etiology of the granulomatous process also had a medical history of other autoimmune diseases including primary sclerosing cholangitis, autoimmune hepatitis, primary biliary cholangitis, and inflammatory bowel disease (Table 5). Thus, it is possible that granulomas could have been secondary to these

Figure 2. Photomicrographs of infectious and noninfectious granulomas from 5 different transplant recipients. A, Reactive lymph node with necrotic tissue forming granulomas encircled by epithelioid histiocytes in a patient with bartonellosis. B, Nonnecrotizing hepatic microgranuloma with cytomegalovirus (CMV) inclusion in a patient with CMV hepatitis. C, CMV immunostain from the same patient highlights one positive cell. D, Granulomatous inflammation in a lung biopsy from a patient with cryptococcal pneumonia. E, Grocott methenamine silver (GMS) and (F) mucicarmine stains revealing Cryptococcus spp. G, Nonnecrotizing granulomas in a small bowel resection from a patient with Crohn disease. H, Nonnecrotizing hepatic granulomas and microvesicular steatosis in a patient with drug induced liver injury (hematoxylin-eosin, original magnifications ×400 [A and B], ×20 [D and G], and ×200 [H]; original magnification ×400 [C]; original magnification ×40 [E]; original magnification ×40 [F]).
| Transplant Type | Age  | Sex | Race  | Immunosuppression | Change in Immunosuppression After Diagnosis | Symptoms | Time of Biopsy | Biopsy Site | Final Clinical Diagnosis |
|-----------------|------|-----|-------|-------------------|-------------------------------------------|----------|---------------|-------------|--------------------------|
| Allogeneic HSCT | 72   | M   | W     | Venetoclax, IT MTX | Increased | Asymptomatic | Pretransplant | Lymph node | Sarcoidosis |
| Allogeneic HSCT | 68   | F   | H     | Sirolimus, Tacrolimus | Increased overall; sirolimus removed | Fever Lower respiratory | Posttransplant | Lung | Sirolimus-induced pneumonitis |
| Allogeneic HSCT | 48   | M   | W     | Idarubicin, Cytarabine | Increased | Fever and other systemic symptoms | Pretransplant | Lung | Cryptogenic organized pneumonia |
| Allogeneic HSCT | 70   | F   | W     | None | Unchanged | Asymptomatic | Postransplant | Nasal cavity | Chronic sinusitis |
| Allogeneic HSCT | 45   | M   | W     | Sirolimus | Unchanged | Upper Respiratory Gastrointestinal | Postransplant | Colon | Inflammatory bowel disease |
| Allogeneic HSCT | 66   | M   | W     | None | Increased | Asymptomatic | Postransplant | Colon | Inflammatory bowel disease |
| Allogeneic HSCT | 50   | F   | W     | None | Increased | Gastrointestinal | Postransplant | Colon | Inflammatory bowel disease |
| Allogeneic HSCT | 52   | F   | W     | Ponatinib | Decreased | Asymptomatic | Postransplant | Liver | Drug-induced liver injury |
| Allogeneic HSCT | 28   | F   | W     | None | Unchanged | Dermatologic | Pretransplant | Skin | Ruptured cyst |
| Allogeneic HSCT | 38   | M   | W     | CHOP | Increased | Asymptomatic | Pretransplant | Lymph node | T-cell lymphoma |
| Allogeneic HSCT | 67   | M   | W     | Sirolimus, Tacrolimus | Unchanged | Asymptomatic | Pretransplant | Bone marrow | Unknown—presumed noninfectious |
| Allogeneic HSCT | 72   | F   | W     | Prednisone, Tacrolimus | Unchanged | Asymptomatic | Postransplant | Lung | Unknown—presumed noninfectious |
| Allogeneic HSCT | 68   | F   | W     | None | Unchanged | Asymptomatic | Postransplant | Paraspinal muscle | Unknown—presumed noninfectious |
| Allogeneic HSCT | 49   | M   | W     | Tacrolimus | Unchanged | Asymptomatic | Postransplant | Bone marrow | Unknown—presumed noninfectious |
| Allogeneic HSCT | 70   | M   | W     | Prednisone | Unchanged | Dermatologic Lower respiratory | Postransplant | Eyelid | Superinfected SSTI |
| Allogeneic HSCT | 59   | M   | W     | Prednisone, Mycophenolate | Increased | Lower respiratory | Postransplant | Lung | HMPV pneumonia |
| Allogeneic HSCT | 60   | M   | W     | Prednisone | Decreased | Asymptomatic | Postransplant | Lung | Stenotrophomonas pneumonia |
| Allogeneic + Autologous HSCT | 52 | F | U | Brentuximab vedotin | Unchanged | Fever Lower respiratory | Pre-allo, Post-auto | Lymph node | Bartonellosis |
| SOT Kidney | 61   | F   | AA    | Prednisone, Tacrolimus, Mycophenolate | N/A; discovered at autopsy | Asymptomatic | Postransplant | Lymph node | Sarcoidosis |
| SOT Kidney | 59   | M   | W     | Prednisone, Sirolimus, Azathioprine | Increased overall; sirolimus removed | Fever Lower respiratory | Postransplant | Lung | Sirolimus-induced pneumonitis |
| SOT Kidney | 57   | M   | AA    | Prednisone, Mycophenolate | Unchanged | Musculoskeletal Dermatologic | Posttransplant | Finger | Unknown—presumed noninfectious |
| SOT Kidney | 26   | F   | H     | Prednisone, Tacrolimus, Mycophenolate | Decreased | Fever Gastrointestinal Lower respiratory | Posttransplant | Liver | Disseminated Bartonellosis |
| SOT Kidney | 68   | F   | W     | Prednisone, Tacrolimus, Mycophenolate | Unchanged | Dermatologic | Postransplant | Skin | Blastomyces |
Table 4. Continued

| Transplant Type | Age | Sex | Race | Immunosuppression | Change in Immunosuppression After Diagnosis | Symptoms | Time of Biopsy | Biopsy Site | Final Clinical Diagnosis |
|-----------------|-----|-----|------|-------------------|--------------------------------------------|---------|---------------|-------------|--------------------------|
| SOT Kidney      | 61  | M   | W    | Prednisone Tacrolimus | Unchanged | Asymptomatic | Posttransplant | Skin        | Unknown—presumed noninfectious |
| SOT Kidney      | 60  | M   | AA   | None | Unchanged | Upper respiratory symptoms | Pretransplant | Nasal cavity | Chronic sinusitis |
| SOT Kidney      | 57  | M   | H    | Prednisone Cyclosporine Tacrolimus Mycophenolate | Increased | Systemic symptoms without fever | Posttransplant | Kidney       | Acute interstitial nephritis |
| SOT Kidney      | 73  | M   | W    | Prednisone Tacrolimus Mycophenolate | Unchanged | Asymptomatic | Posttransplant | Skin        | Ruptured cyst |
| SOT Kidney      | 44  | M   | W    | Prednisone Cyclosporine Sirolimus | Decreased | Fever and other systemic symptoms | Posttransplant | Spleen       | Bartonellosis |
| SOT Kidney      | 62  | M   | W    | Prednisone Mycophenolate Sirolimus | Unchanged | Asymptomatic | Posttransplant | Lung        | Cryptococcal pneumonia |
| SOT Liver       | 56  | F   | H    | None | Unchanged | Asymptomatic | Pretransplant | Lung        | Unknown—presumed noninfectious |
| SOT Liver       | 67  | M   | W    | None | Increased | Asymptomatic | Pretransplant | Lymph node | Unknown—presumed noninfectious |
| SOT Liver       | 56  | M   | W    | None | Unchanged | Asymptomatic | Pretransplant | Lung        | Cryptococcal infection |
| SOT Liver       | 16  | F   | W    | Prednisone Tacrolimus Azathioprine | Unchanged | Asymptomatic | Posttransplant | Liver       | Unknown—presumed noninfectious |
| SOT Liver       | 64  | F   | W    | None | Increased | Asymptomatic | Pretransplant | Liver        | Unknown—presumed noninfectious |
| SOT Liver       | 62  | M   | H    | Cyclosporine | Unchanged | Asymptomatic | Posttransplant | Liver        | Unknown—presumed noninfectious |
| SOT Liver       | 67  | F   | H    | None | Increased | Asymptomatic | Pretransplant | Liver        | Unknown—presumed noninfectious |
| SOT Liver       | 69  | M   | W    | Tacrolimus Mycophenolate | Unchanged | Asymptomatic | Posttransplant | Liver       | Primary biliary cholangitis |
| SOT Liver       | 44  | F   | W    | None | Increased | Asymptomatic | Pretransplant | Liver        | Primary biliary cholangitis |
| SOT Liver       | 53  | F   | W    | Sirolimus | Overall unchanged; sirolimus switched to tacrolimus | Asymptomatic | Posttransplant | Lung        | Sirolimus-induced pneumonitis |
| SOT Liver       | 22  | F   | W    | Prednisone Tacrolimus | Unchanged | Gastrointestinal abdominal pain | Posttransplant | Small bowel | Inflammatory bowel disease |
| SOT Liver       | 13  | M   | H    | Prednisone Tacrolimus | Increased | Asymptomatic | Posttransplant | Liver        | T cell–mediated rejection |
| SOT Liver       | 27  | M   | W    | Prednisone Tacrolimus Sirolimus Azathioprine | Increased | Gastrointestinal Abdominal pain | Posttransplant | Liver        | T cell–mediated rejection |
| SOT Liver       | 32  | F   | W    | Tacrolimus | Increased | Fever Gastrointestinal | Posttransplant | Liver        | T cell–mediated rejection |
Table 4. Continued

| Transplant Type | Age | Sex | Race | Immunosuppression | Change in Immunosuppression After Diagnosis | Symptoms | Time of Biopsy | Biopsy Site | Final Clinical Diagnosis |
|-----------------|-----|-----|------|-------------------|--------------------------------------------|----------|--------------|-------------|-------------------------|
| SOT Liver       | 19  | F   | W    | Prednisone Tacrolimus Azathioprine | Increased | Upper respiratory Systemic symptoms without fever | Posttransplant | Liver | T cell–mediated rejection |
| SOT Liver       | 60  | F   | W    | Prednisone Tacrolimus Mycophenolate | Increased | Gastrointestinal Lower respiratory symptoms | Posttransplant | Liver | T cell–mediated rejection |
| SOT Liver       | 70  | F   | W    | Tacrolimus Sirolimus | Unchanged | Asymptomatic | Pretransplant | Lung | Lung adenocarcinoma |
| SOT Liver       | 54  | F   | W    | Tacrolimus Sirolimus | Unchanged | Asymptomatic | Posttransplant | Skin | Infiltrative skin carcinoma |
| SOT Liver       | 65  | M   | W    | Tacrolimus | Unchanged | Asymptomatic | Posttransplant | Skin | Infiltrative skin carcinoma |
| SOT Liver       | 69  | F   | W    | Prednisone Tacrolimus Sirolimus Mycophenolate | Increased | Asymptomatic | Posttransplant | Liver | Autoimmune hepatitis |
| SOT Liver       | 61  | M   | W    | Tacrolimus Mycophenolate | Decreased | Gastrointestinal Abdominal pain | Posttransplant | Liver | CMV hepatitis |
| SOT Liver       | 23  | F   | A    | Tacrolimus Mycophenolate | Decreased | Asymptomatic | Posttransplant | Liver | CMV hepatitis |
| SOT Liver       | 15  | M   | W    | Prednisone Tacrolimus Mycophenolate | Decreased | Asymptomatic | Posttransplant | Liver | CMV hepatitis |
| SOT Liver       | 70  | M   | AA   | Tacrolimus Mycophenolate | Overall unchanged; Mycophenolate stopped, prednisone started | Fever | Posttransplant | Lung | PJP |
| SOT Liver       | 60  | M   | W    | Prednisone Tacrolimus Sirolimus | Increased | Gastrointestinal Lower respiratory symptoms | Posttransplant | Liver | Chronic HCV |
| SOT Liver       | 60  | F   | W    | Tacrolimus Mycophenolate | Decreased | Lower respiratory Systemic symptoms without fever | Posttransplant | Lung | Pneumococcal pneumonia |
| SOT Heart       | 55  | F   | U    | Tacrolimus Mycophenolate | Unchanged | Dermatologic | Posttransplant | Skin | Superinfected SSTI |

Abbreviations: A, Asian; AA, African American; CHOP, cyclophosphamide hydroxydaunorubicin oncovin prednisone; CMV, cytomegalovirus; H, Hispanic; HCV, hepatitis C virus; HMPV, human metapneumovirus; HSCT, hematopoietic stem cell transplant; IT MTX, intrathecal methotrexate; N/A, non-applicable; PJP, *Pneumocystis jiroveci* pneumonia; SOT, solid organ transplant; SSTI, skin and soft tissue infection; W, White; U, unknown.
diseases and unrelated to allograft rejection, even if rejection was concurrently present. However, though it may not be possible to fully exclude these other causes, in all 5 cases, the clinical diagnosis of T-cell–mediated rejection was agreed upon by the treatment teams and was used to guide patient care. Similarly, 1 case of presumed CMV hepatitis was not confirmed histologically as the CMV immunostain on hepatic tissue was negative. While the patient did not have a clear alternate diagnosis, it is not possible to fully exclude other causes. However, the patient was a high-risk host for development of CMV disease, had a compatible clinical syndrome, and experienced marked improvement in serum transaminase levels after treatment with valganciclovir, suggesting that CMV hepatitis was the most likely diagnosis and was favored by consulting specialists. Last, the study is limited by a small sample size of 56 cases and further studies are needed to corroborate our findings. Moving forward, emerging diagnostics such as broad-range ribosomal PCR and metagenomic next-generation sequencing may help further elucidate the underlying etiologies of cryptogenic granulomas. In addition, given that an independent slide review was performed for only a limited number of specimens, there could be additional findings of relevance to the transplant population that future studies could address.

### CONCLUSIONS

Tissue granulomas were uncommon in a large transplant population and mostly noninfectious. Patients with clinical symptoms at the time of granuloma discovery were significantly more likely to have an infectious cause compared with granulomas discovered incidentally, which were unlikely to be infectious. Bartonellosis and CMV hepatitis were the most frequently encountered infectious diagnoses, suggesting that these should be considered when evaluating for infectious etiologies. The approach to newly discovered granulomas in transplant recipients should involve risk stratification primarily based off of patient symptoms and epidemiologic risk factors. Extensive microbiologic testing, including use of MTB PCR may be safely avoided in low-risk patients and granulomas discovered incidentally before transplantation without a clear etiology likely do not require routine surveillance posttransplant.

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