Positive Kveim Test in Patients with Coexisting Sarcoidosis and Human Immunodeficiency Virus Infection*


We present two cases of sarcoidosis complicated by HIV infection. Each case had a different level of sarcoidosis activity and coexisted with either an AIDS-related infection or a HIV-positive state. Manifestations of sarcoidosis were not apparent in the patient with the AIDS-defining opportunistic infection, but were active in the patient with asymptomatic HIV infection. Both patients had granulomatous reactions to Kveim antigen, and one had such a reaction following an AIDS-defining infection. These findings suggest that non-T-cell mechanisms may be involved in granuloma formation in sarcoidosis.

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We present two patients in whom sarcoidosis with Kveim test positivity coexisted with HIV infection. One of the patients developed an AIDS-defining infection (PCP), while the other was asymptomatic. Although it had previously been suggested that the two diseases may be mutually exclusive, four cases of HIV infection complicating sarcoidosis have been previously reported. Both disorders are relatively common in the same age group and coexistence of the two may not be unusual. Of interest was the ability of these two patients to form granulomas in response to intradermal Kveim antigen even though they were both infected with HIV. Granuloma formation has been reported in response to several opportunistic infections associated with AIDS and recent experimental evidence in murine models suggests that non-CD4 mechanisms may be involved in granulomatous processes.

CASE REPORTS

Case 1

A 37-year-old white woman who had sexual contact with a bisexual male first presented to another hospital in July 1987 with a four-month history of progressive fatigue, dry cough, dyspnea and temperature up to 38.9°C. During the three to four weeks prior to admission she also complained of severe proximal muscular weakness and arthralgia. On physical examination, ronchi were heard over the left lung field. The spleen was palpable. A chest radiograph revealed a slight increase in lung markings bilaterally. The heart, pleura and mediastinal structures were within normal limits. The CBC disclosed slight absolute lymphopenia. Blood chemistry values were normal. Serum angiotensin-converting enzyme was elevated at 119.0 U/L (normal for this assay, up to 50.0). A gallium citrate radionuclide scan revealed diffuse grade 2 uptake in the right lung and focal areas of grade 3 uptake in the left lung. Spirometry was normal. Fiberoptic bronchoscopy with transbronchial biopsy was performed. Cytology, routine and AFB cultures and smears and viral cultures all were negative. Pathologic examination revealed multiple perivascular and interstitial, poorly formed, noncaseating granulomas.

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granulomas and interstitial infiltrates of lymphocytes. Electromyography was reported as showing a scattered denervation pattern most consistent with myositis.

A diagnosis of sarcoidosis with pulmonary and muscle involvement was presumed, and prednisone (40 mg by mouth daily) was prescribed with considerable symptomatic improvement. Approximately two months later, the prednisone dosage was tapered to 30 mg/day, and daily fevers (with temperatures up to 40.0°C) recurred. Prednisone dosage was increased to 40 mg/day and then in steps over the next month to 80 mg/day without improvement. Her cough and dyspnea recurred, the latter becoming severe even at rest.

She presented to the Mount Sinai Medical Center for the first time in November 1987, four months after her initial presentation. Physical examination revealed an ill-appearing woman in mild respiratory distress. She was afebrile and the physical examination was unremarkable except for oral thrush. A chest radiograph revealed marked bilateral interstitial infiltrates. Fiberoptic bronchoscopy with transbronchial biopsy was diagnostic for Pneumocystis carinii pneumonia. Granulomas were not seen, and AFB stain and culture were negative. A HIV screen and confirmatory Western blot were positive. She was successfully treated with intravenously administered pentamidine and hydrocortisone. Two months later (after discontinuation of glucocorticoids), the Kveim suspension was implanted. Biopsy four weeks later revealed multiple epithelioid granulomas diagnostic of sarcoidosis (Fig 1). Her course thereafter was marked by chronic diarrhea and wasting. Fifteen months after presentation she developed neurologic findings and a CT scan revealed an enhancing left thalamic mass. Treatment for a presumptive diagnosis of toxoplasmosis (pyrimethamine, sulfadiazine and desamethasone) was unavailing. She expired that same month without recurrence of pulmonary symptoms or signs. Permission for an autopsy was denied.

CASE 2

A 36-year-old woman presented to the emergency room in May of 1989 complaining of a three and a half-week history of raised red nodules on her shins which were not pruritic. Her past medical history was notable for a microcytic, hypochromic anemia thought to be related to bleeding uterine myomata, and episodes of breathlessness treated with beta-adrenergic inhalers. The rash on her anterior abdominal surfaces consisted of numerous hypopigmented annular macules, some of which had erythematous centers with peripheral hypopigmented halos. On palpation the lesions were indurated and not tender. A 4-mm punch biopsy of a lesion revealed multiple well-formed noncaseating granulomas consistent with sarcoidosis. She subsequently complained of increasing dyspnea on exertion. Physical examination revealed blood pressure of 160/105 mm Hg and large, firm, nontender anterior and posterior cervical, axillary and inguinal lymph nodes. Her skin lesions had begun to resolve spontaneously. The Kveim suspension was implanted on her left forearm and when biopsied four weeks later showed multiple well-formed noncaseating granulomas diagnostic of sarcoidosis. A chest radiograph revealed normal lung fields and hilar structures but showed prominent right paratracheal lymphadenopathy. Pulmonary function studies revealed normal spirometry and Deco." The CBC revealed Hb, 9.9 g/dl; Hct, 30.9 percent; MCV, 68.3 dl; MCHC, 32 g/dl; RDW, 17.3 percent; WBC, 6,500/mL. Serum chemistry values were normal except for a mildly elevated alkaline phosphatase level of 168 U/L. The SACE was not elevated. At this time, the patient voluntarily requested a HIV test which proved to be positive and was confirmed by a positive Western blot. The T cell studies showed an absolute lymphocyte count of 2,150/cu mm, with 1,530/cu mm T cells, 900/cu mm CD4 positive cells and 710/ cu mm CD8-positive cells. The patient is currently asymptomatic and receiving prophylactic AZT.

DISCUSSION

These two patients demonstrate the coexistence of sarcoidosis with HIV-related disease of varying severity. Both patients had specific histologic evidence of sarcoidosis. The first patient had granulomas on transbronchial lung biopsy and a positive Kveim test while convalescing from an episode of PCP. The second patient had radiographically evidenced stage I sarcoidosis diagnosed by skin biopsy and a positive Kveim test coexistent with asymptomatic HIV infection. Sarcoidosis became clinically inapparent in the first patient once an AIDS-defining illness intervened (PCP), but was active in the second patient when normal levels of circulating T cells were present. The second patient's findings are consistent with the previously reported case of Wurm et al wherein sarcoid activity persisted in spite of concurrent HIV infection and was successfully treated with corticosteroids. Despite the severe T cell abnormality in the first patient and the HIV-positive state of the second patient, granuloma formation in response to the Kveim antigen was possible. The immunologic findings of the two patients show widely different levels of circulating CD4 cells. Patient 1, with an AIDS-defining infection, had 200 CD4+ T cells/cu mm, while patient 2 had a normal level of 900/cu mm (normal 500 to 1,500/cu mm).

The existence of Kveim positivity in these two patients implies that the mechanism for granuloma formation in sarcoidosis may not exclusively involve helper T cells or may require far fewer functioning CD4+ cells than previously imagined. Skin reactivity to injected sarcoid tissue was first described by Williams and Nickerson in 1935, while Kveim originated the use of histopathologic examination of the cutaneous lesion to confirm the sarcoidal nature of the reaction. Siltzbach and his colleagues refined the techniques involved in producing the test suspension and are credited with perfecting the test as a clinically useful tool. In collaboration with Cohn and others, Siltzbach localized the activity of the Kveim material to membrane-bound dense bodies, although the active agent (like the etiologic agent in sarcoidosis) has never been identified. When validated according to strict guidelines, Kveim testing is capable of great specificity, although sensitivity varies with disease chronicity (and, presumably, activity). We recently

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**FIGURE 1.** Photomicrograph of skin biopsy at site of Kveim antigen injection (case 1). There were well-formed noncaseating granulomas seen best at the left of this field. This constitutes a positive Kveim test (hematoxylin and eosin, original magnification ×100).
reported a false-positive rate of 0.35 percent in 1,133 patients undergoing Kveim testing between 1981 and 1987. 16

Since the Kveim reaction is thought by many to duplicate the pathogenesis of granulomas occurring in sarcoidosis, several investigators have sought to detail the chronology of immunologic events during development of the Kveim skin lesion. These have been summarized by Munro and Mitchell16 and consist of the following: (1) dermal deposition of PAS-positive material, presumably the injected material; (2) interaction of local macrophages with this material accompanied by increased lysosomal hydrolase activity; (3) in about ten days, phagocytic, atypical mononuclear cells appear, and there is endocapillary deposition of complement and immunoglobulins; (4) activated macrophages appear, accompanied by CD4+ (“helper”) T cells; (5) finally, macrophages, giant cells and atypical mononuclear cells transform to epithelioid cells (some of these cells contain material from the Kveim injectate).

The helper T cell, and lymphokines elaborated by it, have been thought to play a central role in the transformation of this cellular response into a granuloma. Indeed, adequate helper T-cell function is generally thought to be a prerequisite for any granuloma formation, and granulomas often are not seen in the AIDS patients with opportunistic infections that routinely cause granulomas in other groups. However, there are reports of granulomas in some opportunistic infections in AIDS, including PCP8 and several mycobacterial and fungal infections,7 even though the patients were severely T cell-depleted. This ability to form granulomas in spite of low T cell numbers and impaired function implies that there may be other non-CD4 mechanisms involved. There is experimental evidence supporting such a concept wherein granulomas have been induced in the lungs of experimental animals in the absence of T cells.9-10 In these T cell-free systems monocytes and monokines including IL-1 and TNF are capable of inducing granuloma formation. Other factors may be involved as well. In another study,11 it has been demonstrated that calcitriol, which is produced from sarcoid macrophages, is capable of inducing proliferation and differentiation of monocytes into macrophage-epithelioid cells, which in turn form granulomas. The potential role of IL-1, TNF and calcitriol in the granuloma formation in response to Kveim antigen in our patients is uncertain but is consistent with other reports which describe granuloma formation with limited or no T cell function.9,11

In this communication we report two patients with sarcoidosis who exhibited positive Kveim reactions despite HIV disease. The ability to form granulomas even in the face of severe immunosuppression secondary to HIV infection suggests that non-CD4 mechanisms may be important in sarcoid granuloma formation.

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Percutaneous Pulmonary Valvuloplasty in an Octogenarian With Calcific Pulmonary Stenosis*  
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