Our data suggest that, compared with TEE, TTE has a low diagnostic sensitivity for both aortic VP and valvular aneurysm. Similarly, TEE correctly identified all patients with mitral VP, with and without associated aneurysm, whereas TTE missed this complication in one-third of the cases. In conclusion, early recognition of VP might improve the patient’s prognosis, thus enabling the clinical outcome to be monitored, the appropriate surgical timing to be chosen, and the need for valve repair or prosthesis substitution to be assessed. In the presence of hemodynamic instability, coupled with suspicion of perivalvular extension of the infective process, multiplane TEE should be performed directly. Finally, the presence of valvular aneurysms and/or significant aortic or mitral valve regurgitation requires careful evaluation.

Stefano De Castro,1 Domenico Cartoni,2 Giulia d’Amati,1 Sergio Beni,2 Jiefen Yao,5 Marco Fiorelli,4 Pietro Gallo,3 Francesco Fedele,2 and Natesa G. Pandian5

1Departments of Clinical Medicine, 2Cardiovascular and Respiratory Sciences, 3Experimental Medicine and Pathology, and 4Neurological Sciences, La Sapienza University, Rome, Italy; and 5New England Medical Center, Tufts University, Boston, Massachusetts, USA

References

Figure 1. High-power view of inflammatory pseudotumor that shows spindle cells dispersed in a sea of plasma cells (hematoxylin-eosin stain; original magnification, ×250).

Inflammatory Pseudotumor Causing Small Bowel Obstruction and Mimicking Lymphoma in a Patient with AIDS: Clinical Improvement after Initiation of Thalidomide Treatment

A patient with AIDS was diagnosed with inflammatory pseudotumor with small bowel involvement. After receiving thalidomide treatment, serum tumor necrosis factor (TNF) and soluble TNF receptor II levels normalized, his constitutional and gastrointestinal symptoms diminished, and the mass lesion shrunk.

Inflammatory pseudotumor is a distinctive pseudosarcomatous inflammatory lesion that occurs most frequently in the soft tissue and viscera of children and young adults [1]. It has a distinctive histological appearance, a generally benign clinical course with multifocal lesions or recurrence in a minority of cases, and confusing nomenclature. Original descriptions of lesions classified as inflammatory pseudotumors focused on their presence in the lung, and many rubrics were generated for the pulmonary lesions [2, 3]. Pseudonyms that frequently appear in the medical literature include the following: inflammatory myofibroblastic proliferation, and inflammatory myofibrohistiocytic proliferation [4].

Patients with inflammatory pseudotumors usually present with such nonspecific systemic symptoms as fever and weight loss. Children may also have growth failure. Common abnormalities revealed by laboratory studies include an elevated erythrocyte sedimentation rate, leukocytosis, thrombocytosis, and hypergammaglobulinemia [5]. These symptoms and laboratory abnormalities may disappear after surgical intervention and are distinct from those of sclerosing mesenteritis, which is usually diagnosed in the absence of constitutional symptoms and laboratory abnormalities [6]. Pathological examination demonstrates that these benign tumors are characterized by...
an intense predominantly plasma cell infiltrate associated with whorls of fibrosis (figure 1). Periodic acid–Schiff staining may be useful to distinguish foam cells from the bacillus-rich macrophages of Whipple’s disease.

The mechanism of action of thalidomide for resolving various inflammatory states is unknown. Thalidomide may be an immunomodulator, particularly in the role of suppressing endogenous cytokines [7]. One of these cytokines, tumor necrosis factor (TNF)-α, has been implicated as an important pro-inflammatory agent in several different disorders, including septic shock, rheumatoid arthritis, Crohn’s disease, adult respiratory distress syndrome, Behçet’s disease, and cancer- and AIDS-associated wasting states [8]. TNF-α can initiate cytokine cascades involving other downstream proinflammatory cytokines such as interleukin (IL)-1, IL-6, and granulocyte-macrophage colony-stimulating factor. Thalidomide has been shown to increase degradation of TNF mRNA and may play a pivotal role in the resolution of various inflammatory states [9].

In view of thalidomide’s potential to modulate certain inflammatory conditions, thalidomide treatment was started for a patient with AIDS after he reported significant gastrointestinal and constitutional symptoms and was diagnosed with a partial small bowel obstruction due to inflammatory pseudotumor of the retroperitoneum.

A 43-year-old heterosexual male was first diagnosed with HIV infection in 1992 but did not receive antiretroviral therapy until 1996, when spiking fevers, severe headache, and an altered sensorium developed. His HIV load was 195,000 copies/mL, and his CD4+ cell count was <10 cells/mm³. He was subsequently diagnosed with disseminated Mycobacterium avium complex (MAC) infection and aseptic meningoencephalitis. With triple antiretroviral therapy and conventional antibiotic therapy for disseminated MAC infection, his CD4+ cell count increased during 30-month period to 185 cells/mm³, and his HIV load decreased to 540 copies/mL.

In early 1998, he had intermittent abdominal pain with cramps and diarrhea, occasional fevers, and weight loss. His laboratory tests were notable for hypergammaglobulinemia and an elevated erythrocyte sedimentation rate. Multiple studies, including abdominal and pelvic CT, upper and lower gastrointestinal endoscopy, and right upper quadrant ultrasonography, were performed but proved unremarkable. Numerous blood and stool specimens for cultures were also collected, but no infectious pathogens were detected.

For the next 4 months, he continued to have intermittent low-grade fevers, occasional night sweats, and slowly progressive weight loss. He was hospitalized after presenting to the emergency department with severe abdominal pain with cramps and 48 h of intractable nausea and vomiting.

His physical examination was notable for temporal muscle wasting coupled with a 15-lb weight loss, dry mucous membranes, moderate abdominal distention and tenderness, and mild hepatosplenomegaly but no peripheral lymphadenopathy. Laboratory studies were notable for hypoproliferative anemia, an elevated erythrocyte sedimentation rate, hypergamma globulinemia (without a monoclonal protein), and modest changes in liver enzyme levels (table 1). Blood, urine, and stool cultures did not reveal bacterial or fungal pathogens. A flat-plate abdominal radiogram suggested a partial small bowel obstruction, and an abdominal CT scan revealed retroperitoneal adenopathy and a bulky 6 × 7-cm mass that encased the small intestine, which resulted in bowel wall edema and a partial obstruction. Aspiration of a matted mass of mesenteric lymph nodes revealed a portion of lymph node that had sheets of pale-staining histiocytes with patchy acute inflammation. A rare well-formed granuloma was also noted. Special staining procedures for organisms or lymphoma were noncontributory.

Despite conservative care, his bowel obstruction did not improve, and several days later, he underwent laparoscopic evaluation. A soft-tissue mass encircled and constricted his small bowel. Multiple biopsies again revealed inflamed fibrous connective tissue and granulation tissue. In addition, rare noncaseating granuloma and abscess-like tissue consistent with a diagnosis of inflammatory pseudotumor were seen (figure 2). No fat necrosis or infiltration of fat by fibrosis was identified in the biopsy specimens to suggest sclerosing mesenteritis, another rare disease entity. Special staining procedures, including acid-fast bacillus staining, periodic acid–Schiff staining, Grocott-Gomori methenamine–silver nitrate staining, and Warthin-Starry staining, were again unrevealing. Despite profound constitutional symptoms and abdominal radiographs that were disconcerting for lymphoma or carcinoma, no malignancy or infectious agent was identified.

The patient received thalidomide (200 mg daily) for the treatment of HIV-associated wasting. It was explained to him that thalidomide possessed antiangiogenic and anticytokine properties that might potentially cause shrinkage of his pseudotumor. Within 1 week, his fevers and night sweats resolved, and

### Table 1. Results of laboratory testing at admission of a patient with AIDS who had inflammatory pseudotumor causing a small bowel obstruction and mimicking lymphoma during hospitalization in 1998.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC count</td>
<td>7000 cells/mm³ (16% lymphocytes, 13% monocytes, and 66% PMNL)</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>31%</td>
</tr>
<tr>
<td>Platelet count</td>
<td>460,000 cells/mm³ (150,000–400,000/mm³)</td>
</tr>
<tr>
<td>Total protein level</td>
<td>11.2 g/dL (6.5–8.7 g/dL)</td>
</tr>
<tr>
<td>Albumin level</td>
<td>4.1 g/dL (3.6–5.0 g/dL)</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate</td>
<td>85 mm/h (≤20 mm/h)</td>
</tr>
<tr>
<td>Serum ferritin</td>
<td>1450 ng/dL (16–323 ng/dL)</td>
</tr>
<tr>
<td>γ-glutamyltransferase level</td>
<td>252 U/L (11–51 U/L)</td>
</tr>
<tr>
<td>Alkaline phosphatase level</td>
<td>300 U/L (41–128 U/L)</td>
</tr>
<tr>
<td>Lactate dehydrogenase level</td>
<td>220 U/L (118–273 U/L)</td>
</tr>
<tr>
<td>Bilirubin (direct) level</td>
<td>0.2 mg/dL (0.0–0.3 mg/dL)</td>
</tr>
<tr>
<td>CD4+ cell count</td>
<td>185 cells/mm³ (460–1450/mm³)</td>
</tr>
<tr>
<td>HIV load</td>
<td>741 copies/mL</td>
</tr>
</tbody>
</table>

NOTE. PMNL, polymorphonuclear leukocytes.

* Normal range or value.
after 4 weeks, he was only rarely having abdominal pain with cramps. Follow-up abdominal CT scans obtained 6 months and 1 year later revealed substantial and continued shrinkage of both the constricting abdominal mass and the retroperitoneal lymph nodes (figure 3). One year after he began thalidomide treatment, he had regained 20 lb, but because of mild peripheral neuropathy, his dosage was reduced to 100 mg daily without complication. Follow-up CT scans obtained 6 months and 1 year later revealed substantial and continued shrinkage of both the constricting abdominal mass and the retroperitoneal lymph nodes (figure 3). One year after he began thalidomide treatment, he had regained 20 lb, but because of mild peripheral neuropathy, his dosage was reduced to 100 mg daily without recurrence of gastrointestinal or constitutional symptoms.

Plasma levels of TNF-α were measured with TNF-α enzyme-amplified sensitivity immunoassay kits (Medgenix; Incster, Stillwater, MN), and levels of soluble TNF receptor II were measured with Hycult ELISA kits (Caltag, San Francisco) [10]. The plasma levels of TNF-α at 45 pg/mL (normal range, 2.8–15.4 pg/mL) and soluble TNF-α receptor type II at 3.6 ng/mL (normal range, 1.4–2.8 ng/mL) were elevated before thalidomide treatment began. Two months later, levels of plasma TNF-α and TNF-α receptor type II decreased to 12 pg/mL and 1.6 ng/mL, respectively, and did not change significantly over 1 year. In addition, there were no important changes in the HIV load or CD4+ or CD8 lymphocyte counts or percentages from baseline values over 1 year.

The term “inflammatory pseudotumor” is descriptive but nonspecific, having been applied to a variety of nonneoplastic tumefacient lymphoid infiltrates in many different sites [11]. The etiology of inflammatory pseudotumor is unknown. The process has been considered to be a reaction to infectious agents, adjacent necrosis or neoplasms, an immunologic lesion, or a myofibroblastic tumor in a continuum from nodular fasciitis to fibrous histiocytoma [12].

In the largest series to date, Coffin et al. [1] described clinical and pathological findings for 84 patients diagnosed with extrapulmonary inflammatory pseudotumor, none of whom were known to be infected with HIV. Sites of involvement included the abdomen, retroperitoneum, or pelvis (61 cases); head and neck, including the upper respiratory tract (12); trunk (8); and extremities (3). Mass, fever, weight loss, pain, and site-specific symptoms were the initial clinical manifestations of inflammation. The lesions ranged in size from 1 to 17 cm (median, 6.4 cm), with the abdominal masses being the largest. Three basic histological patterns were recognized: (1) myxoid, vascular, and inflammatory areas that resembled nodular fasciitis; (2) compact and uniform-appearing spindle cells with intermingled inflammatory cells (lymphocytes, plasma cells, and eosinophils); and (3) sparsely cellular platelike collagen that resembled a desmoid or scar. Clinical follow-up was evaluable for 53 patients, 44 of whom were alive and without evidence of disease. Four patients were alive with persistent inflammatory pseudotumors, and 5 died. The 5 patients who died had complications either due to the location of the lesion or related to treatment (lymphoproliferative lesion after transplantation or sepsis after wound infection). These investigators concluded that inflammatory pseudotumor is a benign, nonmetastasizing proliferation of myofibroblasts with a potential for recurrence and persistent local growth, similar in some respects to fibromatoses.

Davis et al. [12] evaluated 14 patients with inflammatory pseudotumors of lymph nodes by using paraffin-section immunohistochemistry. All biopsies showed proliferation of spindle cells that contained a mixture of inflammatory cells without atypia and involved the hilum and sinuses of the lymph node. Immunostaining showed that the lymphoid infiltrate was predominantly of T cell lineage (except for plasma cells), only a minority of which marked as T helper cells. Nine of the 14 patients had constitutional symptoms, and 1 patient had acute abdominal pain and vomiting.

A MEDLINE search of the literature was conducted with use of the following key words: HIV and/or AIDS, inflammatory (plasma) pseudotumor, inflammatory myofibroblastic tumor, and mesenteric lipodystrophy. The search uncovered a single report of a case [13] that had several features similar to this case. A 44-year-old man infected with HIV for 4 years who had a CD4+ cell count of 272 cells/mm³, abdominal pain and a 10-lb weight loss, and underwent laparoscopic evaluation when various blood and imaging studies proved unrevealing. Although he did not have overt abdominal masses, analysis of biopsy samples of the small bowel mesentery revealed predominantly fat necrosis and fibrosis consistent with sclerosing mesenteritis. The patient received treatment with tamoxifen, because of its reported benefit in treating retroperitoneal fibrosis [14]. Within 10 days after the initiation of therapy he was feeling better, within 1 month he was asymptomatic, and at 12-month follow-up he remained well. The event that triggered the retroperitoneal inflammatory changes that were seen microscopically was not addressed by the investigators, nor did they comment on the mechanism of efficacy of tamoxifen, although they be-
Figure 3. A, CT scan of a patient with AIDS who had inflammatory pseudotumor causing a small bowel obstruction and mimicking lymphoma; the scan shows diffuse abdominal lymphadenopathy with a bulky mesenteric nodal mass (arrow) that displaces and compresses the proximal small bowel. B, Follow-up CT scan showing regression of the mesenteric mass.

believed that it was unlikely to be related to the drug’s estrogen receptor–blocking ability.

Rarely, mycobacterial spindle cell pseudotumor of lymph nodes can show features of idiopathic inflammatory pseudotumor. Two cases of spindle cell pseudotumors in the lymph nodes of patients with AIDS mimicked neoplasms because they were composed predominantly of spindle cells arranged in a storiform pattern [15]. Unlike the pathological findings seen in the case reported here, most of the spindle cells were phagocytic cells that contained large amounts of mycobacteria.

Both the clinical and pathological features of inflammatory pseudotumor can be related to the production of mediators of inflammation. Among these, IL-1 may play an important role [16]. This cytokine is produced mainly by macrophages and has a wide range of local and systemic effects [8]. Locally, IL-1 stimulates proliferation of fibroblasts; extravasation of neutrophils; activation of T and B cells; and proliferation, activation, and increased procoagulant activity of the vascular endothelium. Systemically, it induces production of acute-phase reactants by hepatocytes, proteolysis, and weight loss and neurological disturbance manifested by fever, anorexia, and somnolence.

Among others, Coffin et al. [1] also speculated on the role of IL-6 in the pathogenesis of inflammatory pseudotumor. The clinical syndrome that accompanies plasma cell tumors is akin to the symptoms of angiomatoid malignant fibrous histiocytoma and the plasma cell variants of Castleman’s disease and Hodgkin’s disease, the latter 2 of which are associated with IL-6 production [17–20].

IL-6 is also an important mediator of other neoplastic and inflammatory conditions, including Kaposi’s sarcoma and non-Hodgkin’s lymphoma. In 1 instance, a patient with AIDS developed relapsing fevers, lymphadenopathy, and hepatosplenomegaly and, at autopsy, was found to have Kaposi’s sarcoma, non-Hodgkin’s lymphoma, and Castleman’s disease [21]. In the case reported here, elevated serum IL-6 levels were detected, and I speculated on the role of this cytokine in promoting lymphoproliferation, angiogenesis, and tumor growth. The clinical importance of identifying which cytokines promote inflammation and lymphoproliferations is further underscored by the case of a man with Castleman’s disease and a mesenteric mass who had dramatic resolution in symptoms after he received treatment with murine monoclonal antibody to IL-6 [22].

Recently, the immune-modulating and angiogenesis-inhibiting activities of thalidomide have led to a revival of interest in this drug. Experience with thalidomide, however, dates back to the early 1950s, when it was introduced in Europe as a sedative but banned worldwide in 1962 because of its teratogenic effects. In 1998, thalidomide received approval by the US Food and Drug Administration for limited use within the United States. It continues to garner attention because of a number of anti-inflammatory and immunomodulatory properties mediated primarily by TNF-α inhibition. Thalidomide is currently being used to treat graft-versus-host disease, as an antiangiogenesis factor to shrink tumors, and to modify the clinical manifestations of tuberculosis, erythema nodosum leprosum, systemic lupus erythematosus, Behcêt’s syndrome, and cancer-related cachexia [23, 24].

Thalidomide is also under investigation for the treatment of a number of HIV-related conditions [7]. The conditions of HIV-infected patients with painful and recurrent aphthous oral ulcers, idiopathic esophageal ulcerations, and idiopathic colitis and proctitis have improved during thalidomide treatment [10, 25–28]. Thalidomide’s ability to inhibit TNF-α production may
also be useful for the reversal of HIV-associated wasting syndrome [29, 30]. A randomized, double-blind, placebo-controlled trial showed that clinical signs and symptoms decreased when patients took 400 mg of thalidomide daily [15]. Compared with the placebo-treated group, those patients who received thalidomide gained weight and reported an improvement in sense of well-being. Overall, thalidomide may be beneficial for enhancing patient well-being by reducing TNF-α-induced fever, muscle weakness, cachexia, and malaise associated with HIV-related disease states [31].

Thalidomide may also suppress HIV replication. Infection with HIV has been associated with elevated TNF-α levels, and a correlation between plasma TNF-α levels and viral load has also been reported [31]. TNF-α may stimulate HIV replication by activating nuclear factor κB, an enhancer of HIV transcription required for the establishment of chronic HIV infection. The pharmacological inhibition of TNF-α production by thalidomide is supported by in vitro studies. Exposing macrophages infected with HIV to thalidomide led to a substantial reduction in viral replication and diminution in nuclear factor κB–binding activity [32]. Treatment with thalidomide was found to inhibit the activation of HIV in peripheral blood mononuclear cells of 16 of 17 patients with AIDS, presumably through inhibition of TNF-α synthesis [33].

Elevations in plasma TNF-α levels may be important in the pathogenesis of inflammatory pseudotumors [34]. The therapeutic role thalidomide may have played in the clinical and radiographic improvements seen in this case is a matter of speculation. Inflammatory pseudotumors may regress spontaneously or after biopsy of the tumor mass. In addition, several recent studies have reported conflicting data, with increased TNF-α levels in HIV-infected patients treated with thalidomide [10, 31]. Future clinical studies will need to control for such variables as CD4+ cell count, HIV load, concomitant medication, comorbid illness, and the dose of thalidomide provided to patients. Importantly, in the case described herein, after taking thalidomide, the patient’s constitutional and gastrointestinal symptoms rapidly decreased, and plasma levels of TNF-α and TNF-α receptor II normalized.

How cytokines mediate inflammatory lymphoproliferations and in particular the therapeutic role thalidomide may play in the setting of HIV-associated lymphoproliferations are subjects worthy of further investigation. Because of its teratogenic actions, thalidomide remains contraindicated in women who could become pregnant. Other potential side effects (which may be seen with greater frequency or severity in HIV-infected patients) include peripheral neuropathy, sedation, mood changes, skin rash, and hypersensitivity reactions [23].

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David M. Aboulafia
Division of Hematology/Oncology,
Virginia Mason Medical Center, Seattle, Washington

References

Disseminated *Mycobacterium terrae* Infection in a Patient with Advanced Human Immunodeficiency Virus Disease

*Mycobacterium terrae* has been rarely implicated in human disease and never in patients infected with human immunodeficiency virus (HIV). We describe an HIV-infected patient with disseminated infection by *M. terrae* with pulmonary and cutaneous clinical manifestations. *M. terrae* was isolated from both sputum and urine, and identified by both conventional tests and high-performance liquid chromatography. Clinical and microbiological characteristics of this case are compared with those reported in the literature.

The *Mycobacterium terrae* complex (*M. terrae*, *Mycobacterium nonchromogenicum*, and *Mycobacterium triviale*) includes slow-growing, nonchromogenic mycobacteria (Runyon group III). Up to 18% of isolates of nontuberculous mycobacteria [1, 2] that are recovered from humans are *M. terrae* complex organisms, and these isolates are rarely related to clinical manifestations, thus signifying nonpathogenic colonization. A few cases of human disease that involved joints [3, 4], lungs [5–10], skin [11], gut [12], urinary tract [13], and lymph nodes [14], or appeared as disseminated disease have been described elsewhere [15, 16]. To our knowledge, isolation of *M. terrae* complex has been described only in 1 series of 35 HIV-infected patients (isolation occurred only in 1 case) [1], but clinical manifestations were not mentioned. We describe here an HIV-infected patient with disseminated infection by *M. terrae* that was associated with progressive pulmonary and cutaneous disease. Clinical and microbiological characteristics of this case are compared with those reported in the literature.

**Case report.** A 29-year-old HIV-infected woman had fever (temperature up to 38.5°C) and productive cough. The patient was receiving treatment with didanosine plus stavudine and cotrimoxazole prophylaxis. Physical examination revealed multiple painless, nonitching, papulonodular skin lesions (up to 7 mm) throughout the body, mainly on the face, and slight bilateral enlargement of axillary lymph nodes. Skin tests with multiple recall antigens (Pasteur Mérieux, Lyon, France) and with PPDs from *Mycobacterium tuberculosis* (Biocene; Chiron, Siena, Italy) and nontuberculous mycobacteria (Statens Serum Institut, Copenhagen) were all negative. Results of the usual blood chemistry analyses were normal, except for those that revealed leukopenia, lymphocytopenia, and anemia. The CD4+ lymphocyte count was 19/µL.

Microbiological and serological analyses were performed—particularly repeated cultures of blood, sputum, and urine—for viruses, fungi, bacteria, and mycobacteria. Direct examinations of 3 consecutive sputum samples were negative for acid-fast bacilli (AFB), although 2 of 3 urine samples were positive. This latter finding did not seem pertinent because the patient had no signs of urinary tract involvement. An echocardiogram, a CT scan of the brain, and a chest radiogram were normal. After 2 weeks of continual fever (temperature, 38.5°C), the patient had mild dyspnea, pale skin, and a marked increase of skin lesions. High-resolution CT showed diffuse pulmonary interstitial involvement with a slender miliary pat-