Fever of Unknown Origin in a Patient with Common Variable Immunodeficiency Associated with Multisystemic Granulomatous Disease

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Abstract

Non-caseating epithelioid granulomas have been described in a small number of patients with common variable immunodeficiency (CVID). We report a 26-year-old woman diagnosed with CVID nine years earlier, who developed non-caseating granulomas in the liver, bone marrow and skin. She was referred to our department for a fever of more than one year duration without apparent focus. Extensive search for underlying malignancy or occult infection was unremarkable. Empirical treatment with prednisone was begun and the patient showed a marked improvement. The literature on the association between CVID and non-caseating granulomatous disease, and the differential diagnosis of hepatic granulomas as a cause of fever of unknown origin, is also reviewed.

Key words: common variable immunodeficiency, corticoid, fever of unknown origin, granulomatous disease, sarcoidosis

Introduction

Common variable immunodeficiency (CVID) is a clinically and immunologically heterogeneous disorder. Its etiology is unknown and it is essentially characterized by deficient immunoglobulin production and hypogammaglobulinemia, usually accompanied by decreased serum IgG and IgA levels. About one-half of patients with CVID show T-cell dysfunction including decreased proliferative responses to T-cell receptor stimulation and impaired expression of interleukin-2 (IL-2) and other cytokines (1). Reduced percentages of peripheral B-cells have been described in some subjects with CVID, although there is no convincing evidence for any intrinsic B-cell defect in immunoglobulin synthesis or secretion; however, accelerated peripheral B-cell apoptosis has been demonstrated for some CVID patients (2). CVID is the most common symptomatic primary antibody immunodeficiency syndrome in our region and affects both males and females. Its prevalence has been estimated at 1: 10,000 to 1: 50,000 (1).

This syndrome typically presents as early, recurrent pyogenic infections, particularly in the sinopulmonary and gastrointestinal tracts, and is accompanied by a wide constellation of autoimmune, malabsorptive and neoplastic processes (2). Other infections, suggestive of severe T-cell defects, including Pneumocystis jiroveci, chronic candidiasis, and recurrent orofacial herpes, have been reported in a few patients (2). Symptoms may start at any time from childhood, with the onset most often between the second and third decades of life. Association with multisystemic granulomatous disease is a well-documented complication of CVID, and it is estimated that up to 22% of these patients present sarcoid-like non-caseating epithelioid granulomas in lym-
phoid tissues, solid organs, or skin (3-6). This observation has suggested the existence of a granulomatous or “sarcoïdosis-like” syndrome of CVID that, while close to sarcoïdosis, has its own clinical and histological manifestations (3). We report a new case of the association between CVID and multisystemic granulomatous disease in a patient who presented with fever of unknown origin (FUO).

Case Report

A 26-year-old white female patient was referred to our institution for evaluation of fever of several months’ duration and progressive asthenia. Her medical history recorded recurrent infections of the bronchopulmonary and gastrointestinal tracts (due to *Giardia lamblia* and *Clostridium difficile*) from earliest infancy. She had no familial history of hereditary diseases or susceptibility to infections. In addition she suffered frequent respiratory infections with a torpid evolution and repeated thoracic computed tomography (CT) imaging eventually revealed basal bronchiectasis. Mucoviscidosis and ciliary dyskinesia were ruled out by repeated sweat iontophoresis and bronchoscopic biopsy of the bronchial mucosa. At age 17, during an admission for *Clostridium* infection, she was found to have panhypogammaglobulinemia, with an IgG of 312 mg/dl (normal: 900-1,500 mg/dl), an IgA of 6.6 mg/dl (normal: 140-290 mg/dl), and an IgM of 9.9 mg/dl (normal: 70-250 mg/dl). There was no decreased IL-2 production after T-cell receptor stimulation. IgG antibody responses to commercial diphtheria/tetanus (DT) and *Haemophilus influenzae* type b (Hib)-conjugate vaccines were assessed, with a three-fold increase of the baseline levels four weeks after immunization. Her total B-cell count (CD19+) was 13% (absolute level, 130/μl). CVID was diagnosed and therapy with intravenous immunoglobulin (IVIG) was initiated. One year later bronchiectasis colonization by *Pseudomonas aeruginosa* was confirmed and broad spectrum antibiotics for her episodic pulmonary infections were added to the treatment. Additionally, she experienced recurrent episodes of orofacial candidiases and herpes despite acyclovir prophylaxis. At age 18 tests found impaired liver function and she underwent a biopsy that revealed chronic hepatitis with lymphoid hyperplasia and numerous non-necrotizing epithelioid cellular granulomas (Figs. 1, 2). Subsequent studies identified non-caseating granulomas in the duodenum, bone marrow and skin, consistent with a diagnosis of sarcoïdosis.

She was admitted to our Internal Medicine Department due to a well-tolerated evening fever (38-39°C) of more than one year’s duration, with a partial response to antipyretic treatment; the fever was accompanied by self-limiting infectious processes in the respiratory pathway with increases of her habitual cough and a purulent expectoration. On physical examination her general appearance was good, with dispersive rhonchus and marked hepatosplenomegaly. Laboratory tests revealed decreased white blood cell count (2.9×10⁹/l; normal: 7.5 to 11.5×10⁹/l) but with normal ratios; the basic biochemistry was normal. Immunologic evaluation at this time showed mild lymphocytopenia (781/μl; normal: 1,000-4,000/μl) with the following subset distribution: CD4+ cells: 219/μl (normal: 700-2,000/μl); CD8+ cells: 453/μl (normal: 200-1,000/μl); natural killer (NK) cells: 94/μl (normal: 60-500/μl); B-cells (CD19+): 4/μl (normal: 100-500/μl). The CD4+/CD8+ ratio was 0.48 (normal: 1-2.5). The proliferative response to phytohemagglutinin (PHA), concanavalin A (Con A), and pokeweed mitogen (PWM) was approximately 75% of the normal control values. Despite the absence of B-cells in the patient, autosomal recessive agammaglobulinemia (such as mutations in μ heavy chain gene or λ5/14.1 gene) was ruled out on the basis of the clinical onset of symptoms and concurrent T-cell deficiency. Serum immunoglobulin levels at that time were: 1,070 mg/dl IgG; 6.67 mg/dl IgA, and 5 mg/dl IgM (the patient had received IVIG infusion two weeks earlier). The erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) level were 45 mm/h and 3.44 mg/dl (normal: 0-0.8 mg/dl), respectively. A battery of microbiological stains and cultures failed to identify bacterial, mycobacterial or fungal organisms. Sero-
Figure 3. Chest computed tomography (CT) scan showing bilateral cylindrical bronchiectasis predominantly in the lower lobes.

Figure 4. Abdominal computed tomography (CT) scan showing homogeneous hepatosplenomegaly and minimal retroperitoneal lymph node enlargement.

Figure 5. Bone marrow with normal hematopoietic tissue, displaced in some areas by epithelioid granulomas with minimal necrotic foci. Higher magnification shows an incomplete granuloma (hematoxylin & eosin, ×200 and ×400).

Logical tests for Brucella, Borrelia, Coxiella, Treponema, Leishmania, Toxoplasma, Plasmodium, rubella virus, human immunodeficiency virus (HIV) and hepatotropic viruses were all negative on repeated occasions. Detection of cytomegalovirus (CMV) antigenemia (by expression of pp65 lower matrix protein), and quantification of Epstein-Barr virus (EBV) DNA load were also negative. Hereditary periodic fever syndromes, such as hyper-IgD syndrome (HIDS), familial Mediterranean fever (FMF), or tumor necrosis factor receptor-associated periodic syndrome (TRAPS) were excluded by the sequencing of MVK, MEFV, and TNFRSF1A genes, respectively. The tuberculin skin test (PPD 5 UT) was negative on two occasions, without prior bacille Calmette-Guérin (BCG) vaccination. The chest X-ray was not informative and the thoracic-abdominal CT scan showed the previously described basal bronchiectasis (Fig. 3) accompanied by homogeneous hepatosplenomegalgy and retroperitoneal lymph node enlargement (the largest node was 1.2 cm) (Fig. 4). In order to discard an underlying infectious or neoplastic condition (gastric or lymphoproliferative), samples were obtained from the duodenum and bone marrow, confirming the presence of noncaseating granulomas with no evidence of infection or malignancy (Fig. 5). The microbiological processing of the samples for fungi, parasites and mycobacterium was negative (Ziehl-Neelsen, periodic acid-Schiff and silver stains), as were the immunohistochemistry (IHC) analyses for human herpes virus type 8 (HHV8). Bone marrow culture for Leishmania spp. on Novy-McNeal-Nicolle (NNN) medium was also negative. The transthoracic echocardiography showed no images suggestive of valvular vegetations. A gallium-67 citrate whole-body scan also revealed no sign of pathological tracer uptake, with the exception of the mild hepatomegaly. Two consecutive angiotensin-converting enzyme (ACE) determinations showed a level rise from 30.9 to 87.3 U/l (normal: 8-52 U/l). The 24-hour urinary calcium excretion was 40 mg (normal: 0-300 mg). With the suspicion that the underlying cause of the febrile syndrome was a sarcoidosis-like or granulomatous form of CVID, steroid therapy (1 mg/kg/day of prednisone) was initiated. Her fever immediately remitted, and after one month of treatment, the ESR was 10 mm/h, and ACE and CRP levels returned to normal (15.9 U/l and 0.65 mg/dl, respectively). Presently, at 18 months of follow-up the patient continues to be afebrile and practically asymptomatic; she has had no significant sino pulmonary infections and her pulmonary function remains stable. A recent immunologic evaluation was similar to previously reported values. Her current therapy includes 2.5 mg prednisone on alternate days, with the purpose of discontinuing it as soon as possible, and anti-fungal and antibiotic prophylaxis (itraconazole and cotrimoxazole) added to the monthly immunoglobulin replacement therapy (400-500 mg/kg/mo).

Discussion

This case presents a diagnostic dilemma in which prolonged fever without an apparent infectious or neoplastic cause appears in a patient with CVID and previously diagnosed liver, skin, intestinal and bone marrow non-caseating granulomatous disease. It is well known that sarcoid-like, non-caseating granulomas occur frequently in patients with
CVID. Previous studies have reported a prevalence that ranges between 8% and 22% in CVID patients, but the actual incidence remains unknown (3, 6). Nevertheless, the true relevance and pathogenic connection between these phenomena are still uncertain, and there is considerable controversy as to whether granulomatous disease seen in the context of CVID should be considered an atypical expression of sarcoidosis or a separate clinical entity, also described as a “sarcoidosis-like” CVID syndrome (6-8).

The underlying pathophysiology of the association remains obscure. The absence of granulomatous disease in other primary immunodeficiencies that are concomitant with antibody deficit (such as X-linked agammaglobulinemia) has suggested that cellular immunity plays an important role. Antigen-processing defects or deregulation of inflammatory cytokine expression (IL-2 and IFN-γ) by T-cells may lead to an inappropriate macrophage and epithelioid cell activation (3, 4). Different autoimmune diseases are frequently associated with granulomatous CVID (over 50% of patients), particularly rheumatoid arthritis, haemolytic anaemia or primary biliary cirrhosis (Table 1). This elevated co-occurrence also suggests some defect in cell-mediated immunity as a possible link between both entities (3).

As in sarcoidosis, the search for a hypothetical antigenic, infectious or environmental etiology for granulomatous disease in CVID has been unsuccessful (4). Patients with CVID might be more susceptible to certain transmissible agents who have been implicated as potential causes of sarcoidosis (e.g. mycobacteria, Borrelia burgdorferi, Propionibacterium acnes…). Nevertheless, some authors have suggested that HHV8 infection may be involved since patients with granulomatous disease and CVID are at high risk for developing lymphoproliferative disorders (9). HHV8 has the capacity to cause B-cell, lymphoproliferative diseases, particularly in secondary immunodeficiency (such as HIV-1 infection or bone marrow transplantation). There is a higher prevalence of HHV8 infection in CVID patients than in healthy controls and the prevalence is even higher in CVID patients with systemic granulomatous diseases (4). We have not been able to confirm this hypothesis in the present patient since IHC for the HHV8 proteins on the available biopsy specimens (bone marrow, liver or lymph node) was negative, prompting us to consider other etiologic mechanisms. On the other hand, there is a recent report of a previously healthy patient who developed non-caseating granulomatous lesions associated with CVID shortly after a Toxoplasma gondii infection (10). The present patient’s serological test was negative for this disease and no tachyzoites were identified in the histological samples, which also discounts this possible association.

The non-caseating granulomas associated with CVID are histologically indistinguishable from those of sarcoidosis, although different organs are affected. Pulmonary affection occurs in 10% of granulomatous CVID patients versus 90% of sarcoidosis patients, and the respective prevalence of liver disease is around 60% and 80% (6, 8). Caseating granulomas are quite rare and have been described in only a few patients with CVID, and pose the additional challenge of thoroughly ruling out infectious etiology (11, 13). Splenomegaly is a frequent clinical finding in granulomatous CVID (89% of patients) and splenic granulomas are documented in 20% of cases, while only 5% to 15% of sarcoidosis patients show splenomegaly on physical examination (4). Erythematous, indurated papules and plaques with an acral distribution may be found in other primary immunodeficiencies (such as chronic granulomatous disease or ataxia telangiectasia) and also appear in patients with CVID and granulomatous disease (11-13). Patients with sarcoidosis typically show hypergammaglobulinemia, whereas the hallmark findings of CVID are the markedly diminished serum immunoglobulins and impaired antibody responses (8). The level of serum angiotensin-converting enzyme (ACE) and the classic Kveim-Siltzbach test are non-specific and not helpful in characterizing either entity (7, 8). Consequently CVID should be suspected in patients with sarcoidosis who do not exhibit the characteristic hypergammaglobulinemia and who have a history of recurrent infections.

Systemic granulomatous disorders, like sarcoidosis, granulomatous hepatitis or inflammatory bowel disease, are infrequent but well documented causes of fever of unknown origin (FUO) (14-18). For instance, fever is a common accompaniment of hepatic granulomas and occurs in as many as 75% of cases (16, 17). It is a result of the release of IL-1 and other endogenous pyrogens from activated mononuclear phagocytes found in the granulomas. Once an infectious etiology has been excluded, oral prednisone generally results in a prompt defervescence and symptomatic improvement (16, 18, 19). Nevertheless, in most series of FUO in the literature, granulomatous diseases make up less than 5% of diagnostic categories, usually labeled as “collagen diseases” or “inflammatory disorders” (14). The present patient presented with prolonged fever, and her underlying impaired immune status led us to include a wide range of entities in our differential diagnosis, particularly infections that have an inflammatory granulomatous pattern (including tuberculosis and non-tuberculous mycobacterial infection) or lymphoproliferative diseases. Serological testing for infectious diseases may be unreliable in antibody-deficient patients; however, direct cultures or nucleic acid identification techniques (i.e., EBV) were persistently negative in our case. The optimal treatment for CVID with widespread granulomatous afecta-

| Table 1. Prevalence of Autoimmune Disorders Frequently Associated with Granulomatous Common Variable Immunodeficiency (CVID) in Two Large Series of Patients (3, 6) |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Autoimmune haemolytic anaemia | 4/17 (23.5%) | 5/30 (16.6%) | \    | \    |
| Immune thrombocytopenic purpura | 5/17 (29.4%) | \    | \    | \    |
| Primary biliary cirrhosis | 1/17 (5.8%) | 1/30 (3.3%) | \    | \    |
| Rheumatoid arthritis | 1/17 (5.8%) | 1/30 (3.3%) | \    | \    |
| Pernicious anaemia | 1/30 (3.3%) | \    | \    | \    |
ation is still uncertain; periodic administration IVIG, the mainstay of CVID management, has not been shown to be effective in these cases (4). In patients with severe hypersplenism or refractory haemolytic anaemia, splenectomy has frequently been performed in the past (8). Prolonged corticotherapy has been the most widely studied treatment option, and appears helpful in reducing lymph node enlargement and splenomegaly, improving uveitis and hematological abnormalities (6-8, 20). In most published cases of granulomatous CVID, the use of steroids was not associated with increased frequency of infections or worsening immunological function in patients on IVIG (6). However, immunosuppressive treatment should be avoided in CVID, and it should be emphasized to discontinue corticotherapy as soon as possible. Several corticosteroid cases with an excellent response to anti-TNF-α agents (infliximab) have recently been reported (20, 21), although further studies are needed to confirm the real usefulness of these new biological therapies.

References


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