Hypogammaglobulinemic Patient with Polyarthritis Mimicking Rheumatoid Arthritis Finally Diagnosed as Septic Arthritis Caused by Mycoplasma hominis

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Abstract

Hypogammaglobulinemia is a reduction or absence of immunoglobulin, which may be congenital or associated with immunosuppressive therapy. In addition to infectious diseases, autoimmune diseases have also been reported in patients with hypogammaglobulinemia. A 26-year-old man with hypogammaglobulinemia had multiple joint pain and swelling with erosive changes in the proximal interphalangeal joint of the right middle finger on X-ray film, mimicking rheumatoid arthritis (RA). As polyarthritis remained after immunoglobulin replacement therapy and there was no finding indicating any infection at that time, a diagnosis of RA was made. Prednisolone and etanercept were started. However, his polyarthritis did not improve and he developed meningitis and massive brain ischemia. Finally, a diagnosis of disseminated Mycoplasma hominis infection was made. The differential diagnosis of polyarthritis in patients with hypogammaglobulinemia should strictly exclude Mycoplasma infection by culture with special media or longer anaerobic culture, and molecular methods for mycoplasma.

Key words: hypogammaglobulinemia, septic arthritis, rheumatoid arthritis, Mycoplasma hominis, erosions

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Introduction

Hypogammaglobulinemia is a heterogeneous disorder characterized by markedly reduced immunoglobulin, including X-linked agammaglobulinemia (XLA), common variable immunodeficiency (CVID), selective immunoglobulin (Ig) A deficiency, immunoglobulin deficiency with increased levels of IgM, and autosomal recessive agammaglobulinemia. These patients with no or decreased levels of gamma globulin are vulnerable to infection with encapsulated bacteria, such as Streptococcus pneumoniae and Haemophilus influenzae, mycoplasma, and ureaplasma.

Autoimmune disorders associated with hypogammaglobulinemia have also been reported, such as rheumatoid arthritis (RA) (1-3), juvenile idiopathic arthritis (JIA) (4, 5), ankylosing spondylitis (6), and systemic lupus erythematosus (SLE) (7). The prevalence of arthritis was reported to be 10-30% in patients with hypogammaglobulinemia (8), and some patients were reported to require disease-modifying antirheumatic drugs (2, 3). Here, we report a hypogammaglobulinemic patient with polyarthritis associated with erosive changes seen on X-ray film mimicking RA, in whom a final diagnosis of Mycoplasma hominis infection

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Case Report

A 26-year-old man was admitted to a local hospital because of a 2-month history of back pain, and polyarthralgia of the bilateral hips, knees, shoulders, and the proximal interphalangeal (PIP) joint of the right middle finger. He had suffered pneumonia and pleuritis 1 year prior to admission. Paracentesis of pleural effusion revealed an elevated lymphocyte-dominant cell count and a slightly increased adenosine deaminase (ADA) level (52 IU/L). Culture of pleural effusions was negative for bacteria and mycobacteria, and polymerase chain reaction (PCR) analysis for tuberculosis was negative. Because his ADA was slightly elevated, he had been treated with antituberculosis drugs; however, no further examinations or therapy were performed as his gamma globulin fraction was so low (4.7%). He had no other past medical history and no family history of immunodeficiency. His temperature was 38.2°C. The PIP joint of the right middle finger was swollen and he had pain in the bilateral elbows, knees, shoulders, and hips. A subcutaneous nodule was present on the left wrist, which was neither tender nor red. His white blood cell count was 14,100/μL (neutrophils 80%, eosinocytes 3%, lymphocytes 8%, monocytes 9%) and C-reactive protein was 18.64 mg/dL. Total protein was 5.1 g/dL and the gamma globulin fraction was 4.4%. His kidney function was normal, but he had mild liver damage (alanine aminotransferase level 118 IU/L). No white blood cells were detected in urine. Rheumatoid factor, anti-CCP antibody, and anti-nuclear antibody were negative. The immunoglobulin levels were markedly decreased (IgG 228 mg/dL, IgA 8 mg/dL, and IgM 1 mg/dL). B cells in peripheral blood were not detected using monoclonal antibodies to CD19 and CD20 (<1%). However, the levels of Bruton’s tyrosine kinase (Btk) proteins expressed on monocytes were normal, as determined by flow cytometry. His hypogammaglobulinemia was not due to mutations in Btk proteins (i.e., XLA) and was not classified as typical CVID, because of his B cell deficiency. Intravenous immunoglobulin replacement therapy was started and the IgG level was maintained above 600 mg/dL. A chest X-ray showed that left pleural effusion and pleural thickening remained; however, the extent of pleural effusion was not so severe that paracentesis was required. Fluid was observed around the left hip joint on computed tomography. Echocardiography did not detect any abnormalities, including vegetations. Antibodies to Mycoplasma pneumoniae, cytomegalovirus, and Epstein-Barr virus were negative. The results of blood, urine, and knee arthrocentesis stab cultures were all negative. White blood cell count in synovial fluid was 3+, and no uric acid or calcium pyrophosphate crystals were detected. S. pneumoniae, but not mycobacteria, were detected in sputum culture. The results of the Quantiferon® TB-Gold test for tuberculosis were negative. Septic arthritis was initially suspected, although no pathogen was detected. Imipenem/cilastatin sodium and pefloxacin mesilate were started, but these treatments were not effective. Open synovial biopsy of the PIP joint of the right middle finger was performed and infiltration of monocytes and macrophage in the synovium was observed, but neither plasma cells nor B cells were detected (Fig. 1). No villous proliferation of synovial tissues or lymph follicles was detected. M. pneumoniae, Chlamydia pneumoniae, and Legionella pneumophila were not detected from biopsy tissue by a PCR-based method. Active synovitis was confirmed, but its cause was unclear. The patient was admitted to our hospital two weeks after admission to the previous hospital. He had morning stiffness and tenerness in the bilateral shoulders, wrist, knees, hips, ankles, and the PIP joint of the right middle finger with swelling; however, neither redness nor a hot sensation was notable, as is usually observed in infectious arthritis. His hip pain was so severe that he could not move the hip joints and was bedridden. Erosion and joint space narrowing of the PIP joint of the right middle finger were observed (Fig. 2). Mifamurtide, panipenem, and vancomycin were ineffective. Since polyarthritis with radiographic erosion without evidence of infection persisted, despite an IgG level above 600 mg/dL, and his symptoms satisfied the American College of Rheumatology classification criteria for rheumatoid arthritis (RA), prednisolone (PSL) was started at 10 mg/day. His CRP levels decreased from 16.9 mg/dL to 8.1 mg/dL and his symptoms showed slight improvement but still persisted. Etanercept (ETN; 25 mg) was administered subcutaneously, after administration of isoniazid for 2 weeks. The patient’s arthralgia and joint swelling showed further improvement. One week after the first administration of ETN, the patient showed an elevated fever above 38.5°C. The antibiotics doripenem and arbekacin were started and ETN was discontinued. An open biopsy of the right hip was performed, and joint destruction was severe, but the fluid around the joint did not have a pus-like appearance. He had suffered from a headache, and meningitis was suspected. Panipenem, voriconazole, linezolid, and acyclovir were started. Bacteria that grew very slowly in anaerobic culture (more than 5 days) were observed from spinal tap and fluid from the right hip, and M. hominis infection was determined by 16S rRNA sequence analysis. Disseminated M. hominis infection could not be controlled and the patient died. Autopsy revealed a microabscess into which neutrophils had infiltrated. Macrophages and T cells were histologically observed in the lung, left hip joint, lymph nodes, endocardium, myocardium, testis, liver and kidney. This prominent peripheral bronchiolar and peribronchiolar infiltration of inflammatory cells indicated bronchial pneumonia. Suppurative meningitis, chronic stage, was indicated, showing infiltration of macrophages and T lymphocytes in the entire subarachnoid space of the cerebrum and spinal cord. Despite the fact that no pathogens, including Mycoplasma spp., were detected by staining, M. hominis was cultured from hip synovial fluid, spinal fluid and blood, and disseminated M. hominis infection was compatible with the autopsy findings.
Discussion

We report here a patient with hypogammaglobulinemia and polyarthritis accompanied by erosive changes on X-ray film similar to RA. The ultimate diagnosis in this case was septic arthritis caused by *M. hominis*.

Primary hypogammaglobulinemia, impaired production of antibodies, is caused by defects in B cell maturation or the interaction of B cells with T cells. XLA is characterized by recurrent upper and lower respiratory infections in infants, and is due to abnormalities of Btk protein, resulting in defective B cell maturation. This case was not diagnosed as XLA because Btk protein in monocytes remained within the
normal range, despite the reduced levels of B lymphocytes in blood and tissues. Furthermore, the patient had no history of recurrent bacterial infection in childhood and he had no relevant family history. CVID is characterized by reduced immunoglobulin levels, despite the presence of B cells, which differed from the observations in the present case. Autosomal recessive agammaglobulinemia was also considered, which is characterized by mutations in genes essential for B cell maturation other than Btk; however, there was no typical family history of the autosomal recessive pattern of inheritance in this case. Indeed, the pathogenesis of hypogammaglobulinemia was not evident in this case.

The prevalence of arthritis in patients with hypogammaglobulinemia has been reported to range from 10% to 30% (8), and several types of arthritis can occur (2, 9). While septic arthritis due to atypical organisms is important, aseptic arthritis has been reported in patients with hypogammaglobulinemia. Chronic arthritis in such patients is usually without erosions and responds well to gamma globulin replacement therapy, which is distinct from classic RA (2, 9) and may be classified as a reactive arthritis (2). Furthermore, several reports have described arthritis due to autoimmune disorders, such as RA (1-3), JIA (4, 5), and spondyloarthritis (6) associated with hypogammaglobulinemia, and only T cells can cause synovitis and arthritis (1, 3). Gold, sulfasalazine, prednisolone, methotrexate, and non-steroidal anti-inflammatory drugs (NSAIDs) are effective in these cases. The present case satisfied the new 2010 criteria for RA classification (10): furthermore, erosive changes and joint space narrowing mimicking RA were observed. Since joint destruction can develop in both RA and septic arthritis, infection should be strictly excluded in the differential diagnosis, especially in hypogammaglobulinemia patients.

With regard to septic arthritis in hypogammaglobulinemic patients, the most frequent pathogens are Staphylococcus aureus, high-grade encapsulated organisms, such as S. pneumoniae and H. influenzae, Mycoplasma species, and Ureaplasma species (2, 11). Furr et al reported 21 septic arthritis patients with hypogammaglobulinemia; Mycoplasma or Ureaplasma species were isolated from eight (38%) (12). Among several Mycoplasma and one Ureaplasma species that are pathogenic to humans, M. hominis and U. urealyticum are strongly associated with arthritis in immunosuppressed patients and those with hypogammaglobulinemia (13).

Septic arthritis due to M. hominis has been reported previously, and most patients were receiving immunosuppressive therapy for SLE, post-organ transplantation, leukemia, or underlying immunosuppressive disease such as hypogammaglobulinemia or diabetes mellitus (14-20). Arthroplasty and ligament repair were also underlying conditions (14, 15). Previous reports of septic arthritis due to M. hominis showed that monoarthritis or oligoarthritis of large joints such as the knee, shoulder and/or hip first occur (14-20) and then polyarthritis develops in the small joints (16, 18). In the case presented here, two months had passed before admission to hospital and polyarthritis in six large (bilateral hips, knees, shoulders) and one small (thePIP joint of the right middle finger) joints had developed. Finally, his arthritis spread to eight large (bilateral shoulders, knees, hips and ankles) and three small (the PIP joint of right middle finger and bilateral wrists) joints. Since rheumatoid arthritis typically affects many small joints first, occasionally associated with arthritis of large joints, the distribution and progression of arthritis in this case differed from that in typical RA. On the other hand, septic arthritis due to bacteria or mycobacterium usually affects monoarticular joints, most frequently the knee in bacterial septic arthritis (21) and the hip in mycobacterium arthritis (22). However, arthritis may spread to polyarticular joints if appropriate therapy is not performed. Thus, septic arthritis should be carefully excluded in patients with long lasting polyarthritis, especially when large joints are predominantly affected.

Isolation of Mycoplasma species by routine culture is either not possible or very slow, which tends to delay the diagnosis (15). In the present case, M. hominis was detected in anaerobic culture on day five. The cultures were stopped after three days in the previous hospital, yielding a false negative result. Routinely-used anaerobic culture media are useful for detection of M. hominis if culture is continued for more than five days. A special culture medium, pleuropneumonia-like organism (PPLO) broth, is the best way to detect Mycoplasma species. Molecular methods are required for identification of M. hominis, which are not routinely performed.

M. hominis is commonly isolated from the normal genitourinary tract, and genital colonization increases in proportion to sexual experience. Furthermore, 1-3% of respiratory secretions from healthy individuals are colonized with M. hominis (23). The present patient had no medical history and no pyuria. Since pneumonia and pleuritis preceded septic arthritis and autopsy revealed bronchiolar pneumonia, the original site of M. hominis infection was predicted to be the lower respiratory tract.

Tetracyclines, including doxycycline, are generally the first choice for treatment of M. hominis infection. However, streptomycin, clindamycin, and quinolones are also used in cases in which tetracyclines are not sufficiently effective (14, 24). Many antibiotics were used in this case, including a quinolone (pazufloxacin) but not tetracycline. M. hominis has also been reported to be moderately susceptible to rifampicin (14), and the pleuritis in this case was somewhat improved by antituberculosis therapy. Since the diagnosis of mycoplasma infections is difficult and slow (15), tetracycline treatment should be administered to patients with hypogammaglobulinemia showing arthritis, pleuritis, meningitis, or any other diseases that may be caused by mycobacterium infection.

Here, we report a hypogammaglobulinemic patient with polyarthritis, accompanied by erosive changes on X-rays, mimicking RA, in whom a final diagnosis of M. hominis infection was made. Septic arthritis caused by Mycoplasma
species should be excluded using special culture media and molecular methods in hypogammaglobulinemic patients. Furthermore, tetracycline can be a useful diagnostic and therapeutic option in such cases.

The authors state that they have no Conflict of Interest (COI).

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