

CASE REPORT

Good's Syndrome with *Pneumocystis jiroveci* Lymphadenitis and Pure Red Cell Aplasia

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ABSTRACT

Pneumocystis jiroveci lymphadenitis is a rare manifestation of extrapulmonary pneumocystosis. A case of recurrent infection with lymphadenitis caused by *Pneumocystis jiroveci* in a middle-aged patient is described. He presented with prolonged fever, recurrent diarrhea, and severe anemia required frequent blood transfusion recognized to be Good's syndrome. Cervical lymph node biopsy revealed caseating granulomas and presence of organisms morphologically consistent with *Pneumocystis spp.* Bone marrow biopsy was compatible with pure red cell aplasia associated with Good's syndrome. According to our knowledge, it is the first case diagnosed with Good's syndrome, *Pneumocystis jiroveci* lymphadenitis and pure red cell aplasia. *J Microbiol Infect Dis* 2016;6(2): 87-91

Key words: Good's syndrome, *Pneumocystis jiroveci* Lymphadenitis, Pure Red Cell Aplasia

Pneumocystis jiroveci lenfadeniti ve saf kırmızı hücre aplazisi ile seyreden Good's Sendromu

ÖZET

Pneumocystis jiroveci lenfadenit ekstrapulmoner pnömositozun nadir görülen bir tutulumudur. Bu yazıda orta yaşlı bir hastada *Pneumocystis jiroveci* neden olduğu tekrarlayan bir lenfadenit olgusu sunuldu. Hasta Good's sendromu olarak tanı konulan uzamış ateş, tekrarlayan ishal ve şiddetli anemi sık kan transfüzyonu ile başvurdu. Servikal lenf nodu biyopsisinde kazeifiye granülomlar ve *Pnömosistis* türleri ile morfolojisi benzeşen bir mikroorganizma saptandı. Kemik iliği biyopsisi Good's sendromu ile ilişkili saf kırmızı hücre aplazisi ile uyumlu idi. Bizim bilgimize göre bu olgu Good's sendromu, *Pneumocystis jiroveci* lenfadenit ve saf kırmızı hücre aplazisinin beraber görüldüğü ilk olgudur.

Anahtar kelimeler: Good's Sendromu, *Pneumocystis jiroveci* lenfadeniti, saf kırmızı hücre aplazisi

INTRODUCTION

Good's syndrome is an association of thymoma and immunodeficiency first described in 1954 by Robert Good. Patients are most commonly present between the ages of 40 and 70 years and usually have low to absent B cells in the peripheral blood, hypogammaglobulinemia, and defects in cell-mediated immunity in the presence of thymoma [1]. These

paraneoplastic syndromes include myasthenia gravis (MG), pure red cell aplasia (PRCA), connective tissue disorders and acquired hypogammaglobulinemia. The patients often present with recurrent infections due to encapsulated bacteria, fungi, and viruses. We presented a patient with thymoma and hypogammaglobulinemia who had recurrent infection and chronic diarrhea, recognized to be Good's syndrome (GS). Extrapulmonary *Pneumocystis jir-*

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oveci infection is rare, regardless of HIV status, and can occur with or without concurrent respiratory tract involvement. *P. jiroveci* has been identified in immunosuppressed patients in lymph nodes, peripheral blood, myocardium, stomach, small intestine, bone marrow, adrenal gland, thyroid gland and retina. Diagnosis of disseminated disease of the non-HIV cases was made antemortem. The major causes of death in patients with non-HIV infected are their underlying disease [2]. Extrapulmonary pneumocystosis should be warranted in the differential diagnosis of granulomatous lymphadenopathy. This case report suggests *P. jiroveci* extrapulmonary pneumocystosis in the patients with Good's syndrome.

CASE REPORT

A 38-year-old man who was previously healthy presented with prolonged fever, recurrent diarrhea, and severe anemia required frequent blood transfusion. He had numerous hospital admissions over a period of 8 months usually for diarrhea, severe anemia and generalized lymphadenitis which were treated with antibiotics. The patient had previously been prescribed with anti-TB medications (isoniazid, rifampicin, ethambutol, pyrazinamide) for treatment of suspected tuberculous lymphadenitis based on a pathological finding of caseating granuloma in lymph node by pathology in another center. Two weeks later, the anti-TB drugs were replaced by ethambutol, streptomycin, ofloxacin after cholestatic jaundice developed. For investigation of a cause of diarrhea, colonoscopy was performed and showed a clean base ulcer at sigmoid colon, a pathological study revealed chronic inflammation with fibrosis, mild eosinophilic infiltration and no granuloma. Multiple cultures from stool, sputum, blood were negative.

On admission, his body temperature was 37.1°C, heart rate was 114/min, blood pressure was 150/100 mmHg, respiratory rate was 28/min and cutaneous oxygen saturation was 84%. Physical examination revealed a thin man with oral candidiasis, generalized lymphadenopathy at both cervical and groin region with 1.5-2 cm in size, firm consistency, pulmonary auscultation showed decreased vocal resonance at right lower lung and left upper lung field with coarse crepitation in both lungs. He had no hepatosplenomegaly. The neurological examination was unremarkable.

Laboratory investigation were performed and revealed a series of abnormal findings. Complete blood count (CBC) revealed the hemoglobin level of 11.8 g/dL, hematocrit 36.5%, Mean corpuscular

volume (MCV) 79 fl, white blood cell count 13,040 cell/mm³ (neutrophils 58.8%, lymphocytes 26.7%, monocytes 12.7%, eosinophils 0.6 %, basophils 1.2%), platelet count 633,000/mm³; blood urea nitrogen (BUN) was 6.5 mg/dL, creatinine was 0.4 mg/dL; total bilirubin was 3.4 mg/dL, direct bilirubin was 3.26 mg/dL, aspartate aminotransferase was 257 U/L, alanine aminotransferase was 262 U/L, alkaline phosphatase was 4,389 U/L, total protein was 4.7 g/dL, albumin was 2.6 g/dL, globulin was 2.1 g/dL; lactate dehydrogenase was 1,081 U/L. A stool examination revealed soft stool consistency and neither cell nor fecal occult blood was detected. A computed tomography (CT) of chest showed heterogeneous enhancing soft tissue mass within anterior mediastinum adjacent to main pulmonary trunk 2.6x1.5 cm in size, consistent with thymoma, multiple calcified lymph nodes at prevascular, bilateral paratracheal, subcarinal, paraaortic, subaortic, both hilar and left supraclavicular regions, multifocal patchy consolidation at left upper lung, right upper lung and both lower lungs, bilateral pleural effusion.

Cervical lymph node biopsy revealed caseating granulomas with focal dystrophic calcification and presence of organisms morphologically consistent with *Pneumocystis* sp. as shown in figure 1. No acid fast bacilli, bacteria and malignancy was found. Sequence analysis of the fungal internal transcribed spacer (ITS) region amplified the organism from the infected cervical lymph node showed 98% homology with *P. jiroveci* thus reported as *P. jiroveci*. CT guided biopsy of anterior mediastinal mass revealed benign epithelial cells mixed with small lymphocytes compatible with thymoma, type AB shown in figure 2. Bone marrow biopsy was compatible with pure red cell aplasia associated with Good's syndrome as shown in figure 3 and 4. The patient presented with recurrent infection (*Escherichia coli*, *Salmonella* group C septicemia and *P. jiroveci* lymphadenitis) suggestive of immunodeficiency. Immunophenotyping of peripheral blood lymphocytes showed serum IgG was 276 mg/dl, IgA was 70.8 mg/dl and IgE was 4.42 IU/ml (reference range 548-1,768 mg/dl, 78-322 mg/dl and <100 IU/ml respectively) and markedly reduced numbers of B lymphocytes 2 cells/ul (reference range 140-660 cells/ul), CD4 1,254 cell/ul (33.13%), CD8+ lymphocytes 1,554 cell/ul (41.07%), CD4/CD8 ratio 0.81 (0.65-2.49). Anti-IFN- γ autoantibody was negative. The immunology profiles were consistent with Good's syndrome characterized by the presence of thymoma, hypogammaglobulinemia and depleted B-cells.

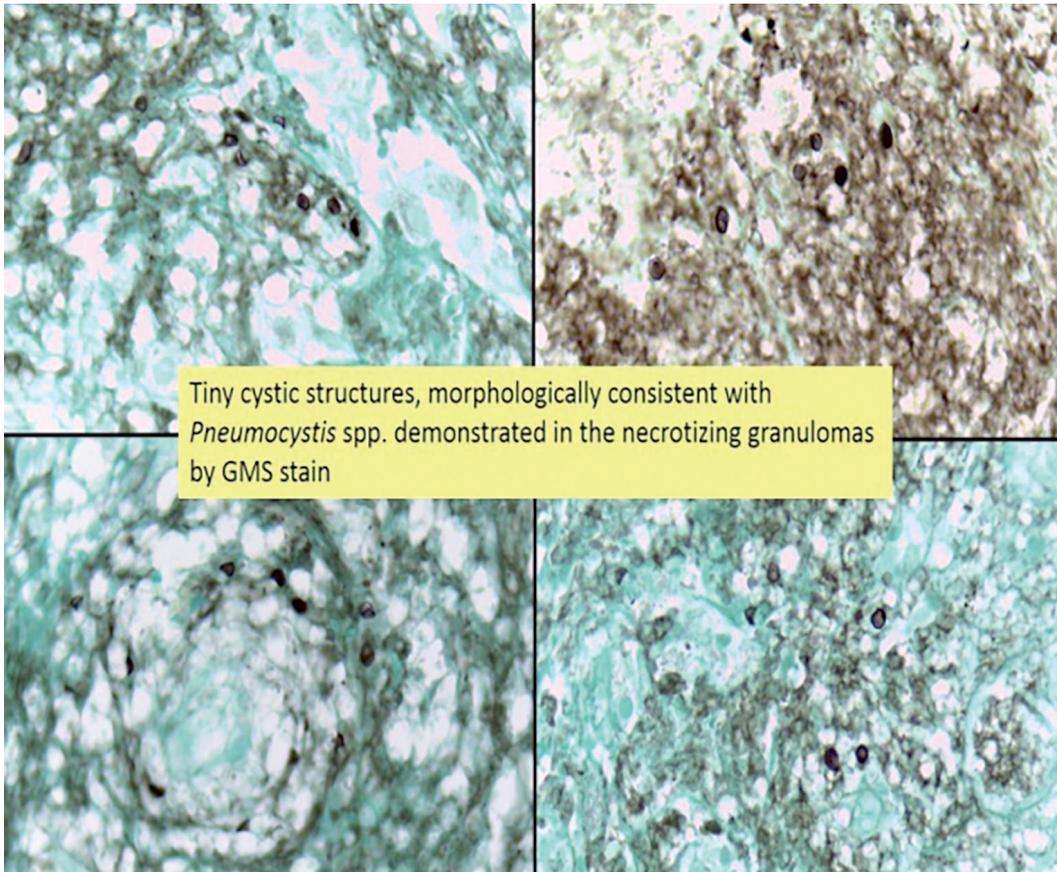


Figure 1. Lymph node biopsy from left cervical: Caseating granulomas with focal dystrophic calcification and presence of organisms morphologically consistent with Pneumocystosis.

Footnote: Tiny cystic structures morphologically consistent with *Pneumocystis* spp demonstrated in necrotizing granulomas by GMS stain

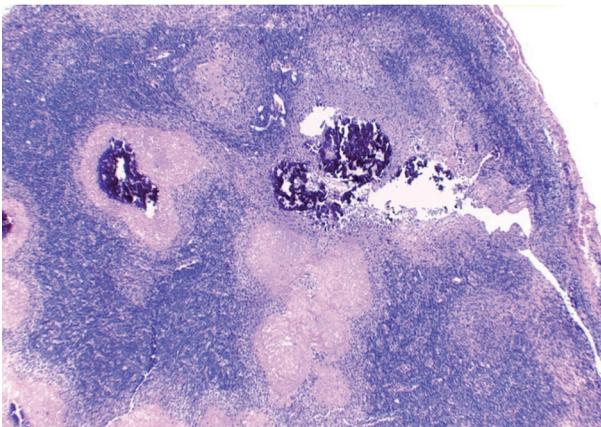


Figure 2. Lymph node is replaced by necrotizing granulomas with scattered calcification

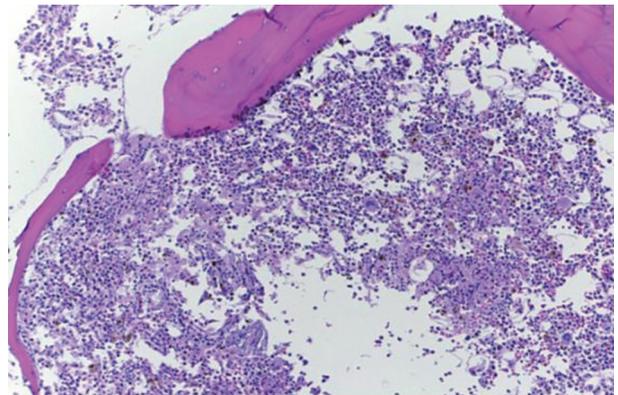


Figure 3. Bone marrow aspiration and biopsy: Moderate to marked hypercellularity,

Myeloid:Erythroid > 10:1, decrease erythroid precursors compatible with pure red cell aplasia.

Footnote: Abnormal bone marrow; moderate to marked hypercellularity due to granulocytic hyperplasia. The bone marrow represent normal megakaryocytes and decrease in erythroid precursors

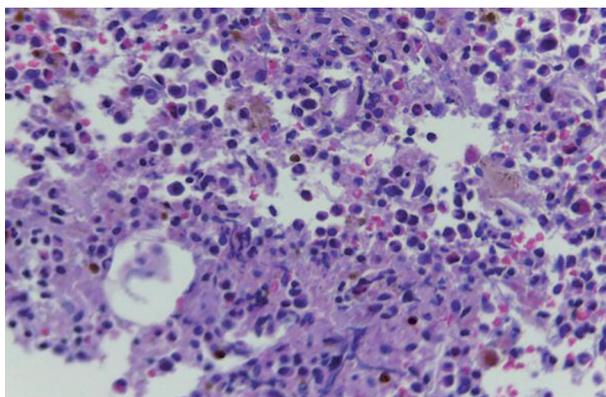


Figure 4. Decrease in erythroid precursors

After diagnosed as Good's syndrome and *P. jiroveci* lymphadenitis, he was treated with intravenous immunoglobulin (IVIg) replacement therapy 0.4 gm/kg to keep IgG trough level greater than 500 mg/dl, trimethoprim-sulfamethoxazole and prednisolone 1 mg/kg/day for 21 days. Subsequently developed *Acinetobacter baumannii* ventilator associated pneumonia and cytomegalovirus viremia which were treated by colistin and ganciclovir respectively. He died with *E. coli* septicemia and candidemia.

DISCUSSION

P. jiroveci is the most common causes and life-threatening opportunistic fungal infection in patients with AIDS, emerging threat to immunocompromised patients without HIV infection [2,3]. Before the AIDS epidemic, there were several widely scattered reports of extrapulmonary pneumocystosis. With the advent of AIDS, extrapulmonary pneumocystosis have been reported. In all 16 of the non-AIDS cases in which *P. jiroveci* were found in extrapulmonary sites, 13 patients had underlying diseases (4 with congenital hypogammaglobulinemia, 1 with thymic aplasia, 1 with cachexia, 2 with hypogammaglobulinemia, 1 with chronic myeloid leukemia, 1 with Hodgkin's disease, 1 with non-Hodgkin's lymphoma, 1 with malignancy and 1 with renal transplant). Extrapulmonary infection was limited to hilar or tracheal lymph nodes in 5 patients. In others 8 patients, the extrapulmonary infection were widespread in thymus, spleen, blood vessels, bone marrow, liver, kidneys, adrenal, gastrointestinal tract, brain, heart, thyroid and hard palate. All of these cases were died. The recommend duration of treatment *P. jiroveci* infection is 21 days in HIV infected patients and 14 days in non-HIV immunocompromised hosts. In non-HIV patients, extended

treatment should be considered in case of severe immunosuppression, high organism burden or prolonged clinical improvement [3].

GS, an adult-onset immunodeficiency associated with thymoma and hypogammaglobulinemia first described in 1954 by Robert Good was rare and accounted for approximately 5% of all patients with thymoma [1,5]. The incidence is 0.15 cases per 100,000 population per year. Affected patients are between 40 and 60 years of age. More than 40% of patients with thymoma had associated immunological abnormalities. The most common manifestation of thymoma were autoimmune diseases, particularly myasthenia gravis (47%) associated with thymoma type B2, pure red cell aplasia (5%) and immunodeficiency (10%) [6]. The immunodeficiency associated with Good's syndrome is characterized by low to absent B cells in the peripheral blood, decrease in all classes of immunoglobulins, abnormal CD4/CD8 T lymphocyte ratio and impaired T cell mitogenic response. The immunodeficiency appears to affect both humoral and cellular components and predisposing to opportunistic infections. The most common pathogens in GS are *Candida* spp., *Aspergillus* spp., multidrug-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *P. jiroveci*, cytomegalovirus and Varicella zoster [7,8]. GS has a high mortality rate of about 44.5% to 57%, mainly because of infectious diseases [9,10]. In this case, a post-mortem examination showed multiple lymphadenopathies in mediastinal, hilar, and mesenteric areas, mediastinal mass with left upper lung and pericardial involvement, gallstones 0.4-0.7 cm in greatest dimension, fluid in peritoneal, fluid and pericardial cavities. The area of generalized lymphadenopathy seemed to correspond with the areas in which *P. jiroveci* was found. The dissemination could have occurred by hematogenous or by lymphatic routes.

To our knowledge, this is the first reported case of pneumocystis lymphadenitis with Good's syndrome. Extrapulmonary pneumocystosis should be warranted in the differential diagnosis of granulomatous lymphadenopathy. This case report suggests to consider *P. jiroveci* infection which can cause extrapulmonary pneumocystosis in the patients who had GS (immunodeficiency state associated with thymoma). GS is associated with a worse outcome than common variable immunodeficiency. The major causes of death in patients with GS consist of infections, autoimmune diseases, and hematologic complications. Immediate treatment of the specific infection with appropriate antimicrobial agents, IVIg

replacement should be considered to reduce the risk of infections, excess use of antibiotic administration and duration of hospitalizations [1]. Recurrent sinopulmonary infections despite of immunoglobulin may be treated with several different prophylactic regimens including azithromycin and clarithromycin [11]. Close collaboration between immunologist, microbiologist and physician is valuable for appropriate management of rare disease of combined B and T cell immunodeficiency.

Declaration of Conflicting Interests: The authors declare that they have no conflict of interest.

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