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Article Type: Case Report

CASE REPORT

Co-existence of Common Variable Immunodeficiency (CVID) with Idiopathic Thrombocytopenic purpura (ITP)

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INTRODUCTION

Common variable immunodeficiency syndrome (CVID) is one of the most common primary immunodeficiency disorders (1). In addition to causing recurrent infections with pathogenic and opportunistic organisms, it is frequently reported in association with autoimmune diseases (1). Idiopathic thrombocytopenic purpura (ITP) is one of the autoimmune diseases that frequently co-exists with CVID (2, 3). The treatment options for ITP, especially if chronic or recurrent, require careful attention in the presence of CVID. This is due to the fact that treatment modalities like corticosteroids, splenectomy, and immunosuppressive drugs may carry a considerable risk of overwhelming infections in patients with CVID (4). We report an adult female patient in whom CVID was detected after the occurrence of ITP.

CASE REPORT

31-year-old lady presented with epistaxis, gum bleeding, and extensive purpura over face, trunk, and both upper and lower limbs. She was afebrile, showed no jaundice, and did not have hepatosplenomegaly or lymphadenopathy or any clinical signs of autoimmune disease. Relevant in the past history was the fact that she had undergone left lung lobectomy for bronchiectasis at the age of 13 years (Figure 1).
On investigations: CBC showed marked thrombocytopenia (platelet count=$12x10^9$/L) with normal hemoglobin (12.1 gm/dL) and WBC count ($6.2x10^9$/L with Neutrophils=$3.98x10^9$/L, Lymphocytes= $1.9x10^9$/L). Biochemically, hepatic and renal profiles, serum glucose, serum electrolytes, calcium, phosphorus, alkaline phosphatase, serum lipids, and serum ferritin were within normal range. However, low levels of serum total proteins (56g/L) and serum globulins (18 g/L) were initially ignored.

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The diagnosis of idiopathic thrombocytopenic purpura was supported by bone marrow examination that showed megakaryocytic hyperplasia.
However, autoimmune profile (ANA, anti DNA, C3, C4, anticardiolipin antibody, lupus anticoagulant, & anti β2 GP antibody) showed normal findings. Tests for antiplatelet antibody and platelet-related immunoglobulin were negative. Coagulation profile was normal. She was treated with i.v. methylprednisolone (1.0 g/ day for 3 days) that showed moderately good response with platelet count rising to $85x10^9$/L.

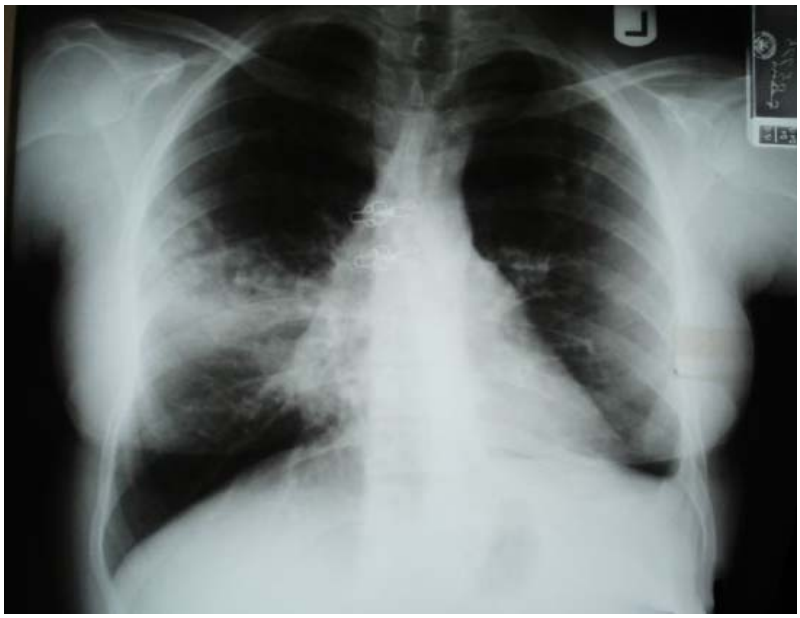

Figure 1. Chest X ray: Old Left lower lobectomy and a recent chest infection

She got three more episodes of severe thrombocytopenia (platelet counts of $10x10^9$/L, $3x10^9$/L, & $9x10^9$/L) in quick succession, all of which responded to pulse therapy with i.v. methylprednisolone. After the last episode, she was given oral corticosteroids (tab. Prednisolone, 0.75 mg/Kg/day), but she developed severe thrush, and soon, multidermatomal Herpes zoster. Serum immunoglobulin assay was done at this stage. It showed severe hypogammaglobulinemia with serum levels of IgG = 2.89g/L (N. = 8-15 g/L) IgA = 0.44g/L (N. = 0.9-3.2g/L) and IgM = 0.51g/L (N. = 0.45-1.5g/L) (Table 1). Although the occurrence of opportunistic infections (oral candidiasis and Herpes zoster) occurred while the patient was under the immunosuppressive effect of steroids, yet with such a low level of IgG and history of bronchiectasis necessitating lobectomy during childhood, the suspicion of a primary immunodeficiency state was raised. HIV infection was excluded by negative ELISA serology, negative western blot, and normal CD4 count. Testing for serotype-specific pneumococcal antibody levels were determined before and after immunization with pneumococcal polysaccharide vaccine, and showed markedly low baseline levels and failure of post-vaccination increment (Data not shown). Tuberculin test was negative in spite of vaccination, and intradermal Candida antigen test was also negative indicating a T cell function defect. Lymphocyte marker studies (Table 1), T- cell functions and cytogenetic studies supported the diagnosis of common variable immunodeficiency syndrome (CVID).
Replacement with intravenous immunoglobulin (IVIG) as 4-weekly sessions "600 mg per Kg per session" was added to steroids for 6 months until the platelet count was

maintained at >50x10^9/L, then programmed complete withdrawal of corticosteroids was made. No more infection episodes were reported with steroid therapy under the cover of IVIG. Later on, single therapy with 4-weekly IVIG "600 mg per Kg per session" has kept both thrombocytopenia and infections under adequate control. Until presently, for a period of more than 3 years, she has neither reported an episode of infection, nor any occurrence of thrombocytopenia.

Table 1. Results of CBC, serum immunoglobulin levels and circulating lymphocytes

CBC			Circulating lymphocytes		Immunoglobulin levels (g/L)	
Hemoglobin		12.1g/dL	CD19 (7-13) %	8%	IgG(8-15 g/L)	2.89
Platelets		12x10^9/L	CD4 (32-59) %	30%	IgA(0.9-3.2g/L)	0.44
WBC	Neutrophils	3.9x10^9/L	CD8 (15-36) %	50%	IgM(0.45-1.5g/L)	0.51
	Lymphocytes	1.9x10^9/L				

N.B: Normal values are given between quotes

DISCUSSION

CVID is one of the most frequently diagnosed primary immunodeficiency diseases in humans (1). The diagnosis is based on: (a) clinical history of recurrent pathogenic and opportunistic infections, (b) hypogammaglobulinemia with decreased serum IgG and IgA levels and generally but not invariably decreased serum IgM, (c) normal or low number of circulating B lymphocytes and normal number of circulating T lymphocytes, (d) defective B lymphocyte function in the form of impaired antibody response to vaccination and normal or defective T lymphocyte function and (e) genetic exclusion of other molecularly well defined hypogammaglobulinemias such as X-linked agammaglobulinemia and hyper-IgM syndrome (1). Facility for molecular analysis is not yet available commercially, but testing for some specific defects such as partial CD40 ligand deficiency (X linked hyper-immunoglobulin M1) and inducible costimulator of activated T cells (ICOS) deficiency, are available in some referral and research centers (5). In the presence of typical clinical and laboratory criteria, diagnosis is otherwise based on exclusion of other known causes of humoral immune defects (1). In addition to recurrent rhino-sinusitis and respiratory tract infections especially bronchiectasis, CVID is associated with an increased incidence of autoimmune diseases and lymphoproliferative malignancy (1). Autoimmune diseases that frequently co-exist with CVID include autoimmune hemolytic anemia (AHA) and ITP (2, 3). In one report of 304 CVID patients, 33 had autoimmune hematologic disease (10.8%); 8 had both ITP and AHA, 17 had ITP, and 9 AHA (3). Sixty-three percent of ITP episodes started prior to the diagnosis of CVID (3). It is recommended that CVID should be suspected and excluded in patients with recurrent ITP/AHA (3,6) .

Corticosteroid therapy is universally accepted as the conventional first line treatment for acute episodes of ITP (7). IVIG is another, but more expensive choice with a shorter lasting effect (7). Patients with non responsive chronic ITP are offered the options of Rho (D) immunoglobulin, splenectomy, Danazol, immunosuppressive therapy with cyclophosphamide or vincristine, and more recently with rituximab or mycophenolate mofetil (8). In patients with CVID, long-term immunosuppressive therapy for associated autoimmune conditions is not recommendable because of the potential risk

of overwhelming infections. As immunization is mandatory in patients with splenectomy (9), and CVID is characterized by lack of antibody response to vaccination (1), splenectomy should be considered a risky treatment option. Nevertheless, Michel et al stated that none of 6 splenectomized patients with CVID and ITP developed a life threatening infection over a 5-6 year period (4). Infections induced by steroids may be controlled under IVIG cover as observed in our case. Pulse therapy with IVIG remains the best option, but unfortunately the benefit may not be long-lasting. In the study by Wang et al, 3 out of 25 patients with ITP and CVID continued to have chronic low platelet counts while on monthly doses of IVIG (3). Longhurst et al reported 4 (Rhesus positive) cases of ITP with co-existent primary antibody deficiency, which remained refractory to steroids and high dose IVIG, though all responded to anti-D immunoglobulin (10). Carbone et al reported a case of CVID with co-existent ITP who proved to be refractory to corticosteroids, IVIG, azathioprine, and vincristine with only a partial response to anti-CD20 monoclonal antibody (Rituximab) (11). Co-existence of chronic ITP with CVID presents a unique challenge. In the majority of cases in whom CVID co-existed with ITP, as in our patient, CVID was detected later than ITP when it surfaced with superadded fungal or viral infections (3, 6). In this setting, the best option for treatment modality of ITP is IVIG in 4-weekly pulses or anti-D immunoglobulin for Rhesus positive cases. In refractory cases, cautious use of combined IVIG with low dose corticosteroids, or anti-CD20 monoclonal antibody (Rituximab) may be warranted.

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