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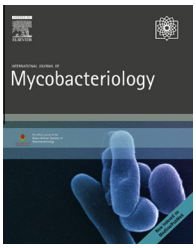

Case Report

Selective immunoglobulin M deficiency in an adult with miliary tuberculosis: A clinically interesting coexistence. A case report and review of the literature

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ABSTRACT

Selective immunoglobulin M (SIgM) deficiency is a rare form of dysgammaglobulinemia. Here we are reporting a 31 year old man with multiple cervical and testicular abscesses who was investigated and found to have miliary tuberculosis (MTB) with primary SIgM deficiency (Serum IgM: 17.4 mg/dL) and was treated aggressively with anti-tuberculous treatment.

Case report

A 31-year-old previously healthy man with an unremarkable clinical history presented with predominant symptoms of fatigue fevers, chills, malaise, anorexia and weight loss 1 year duration. 3 months later, the patient developed painful scrotal swelling on the left side of the scrotum which was drained by a doctor associated with greenish foul discharge and patient was empirically started on broad-spectrum intravenous (IV) antibiotics. The patient was admitted to the Fever Hospital in February 2015 for evaluation of history fever and recurrent scrotal swellings, he was found to have multiple testicular abscesses, which were treated with multiple courses of antibiotics. Despite the medical treatment, the

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patient had another painful swelling on the right side of the neck, so he was subsequently referred to our hospital in April 2015 as a case of recurrent mucocutaneous abscess formation in order to create a diagnosis and treatment plan. He did not have any significant past medical history or surgical history or any risk factors for HIV. There was no history of childhood infections, relatives with opportunistic infections or immunodeficiencies.

Physical examination of the patient on admission was normal except his body temperature was ranging between 38.2 and 39.4 °C and pallor. Cystic tender swelling (4 × 3 cm) was located in the subclavian triangle area, in the supraclavicular region expanding to the occipital triangle. The skin over the swelling was lividly discolored with signs of necrosis associated with generalized small lymphadenopathy. There was scrotal sinus on the left side of the scrotum with signs of necrosis.

At that moment, laboratory tests revealed normal blood sugar, urine analysis and serum biochemistry except mild hypoalbuminemia, mild elevation in liver enzymes and ESR 70 mm/h. There were no abnormalities in WBCs and platelets count except mild lymphocytopenia and microcytic anemia. Serum iron, ferritin were within normal limits.

In routine work up chest X-ray revealed radiologic evidence of MTB and this was confirmed with a positive culture for acid alcohol fast bacilli from a laryngeal swab and blood culture revealed *Mycobacterium tuberculosis*. The BCG scar was present and normal, with negative results of tuberculin test. Neck U/S revealed a bilocular cystic lesion each of them about 2.5 × 3 cm with markedly turbid fluid content. Pus is seen at lower deep cervical to suprasternal notch with multiple enlarged variable size lymph nodes with no abnormal vascularity. Abdominal U/S was normal except mild hepatomegaly. Scrotal U/S and Doppler revealed an abscess about (3 × 1 cm) at the left scrotal neck with hypo echoic area about (3 × 1 cm) is seen at the parenchyma of the testis and another abscess about (5 × 3 cm) is seen at the left thigh (intra muscular). Rt testis showed multiple hypoechoic focal lesions. Screening for malignancy revealed negative results for testicular tumors such as alpha-fetoprotein (AFP), human chorionic gonadotropin (HCG), lactate dehydrogenase (LDH). Serological viral studies revealed negative results of HIV, hepatitis C virus antibodies and hepatitis B surface antigen. Most clinically relevant autoantibodies were checked, but all of them were found to be negative. Laboratory work-up of immunodeficiency was performed (Table 1). The blood cell count, T cells, T cell subsets, B cells, and natural killer cells were within normal limits. Also, we examined the performance of delayed-type hypersensitivity (DTH) antigens using a tetanus toxoid. Our patient was of middle aged. Therefore, our patient is unlikely to have a partial deficiency of adenosine deaminase (ADA). Therefore, no ADA analysis was performed. Interferon y secretion and IFN-yR expression could not be done due to financial causes.

Once the diagnosis of symptomatic sIgMD with miliary tuberculosis was recognized, the patient was treated aggressively with the courses of Isoniazide, Rifampicin, Pyrazinamide, Ethambutol and Clarithromycine to covering for disseminated TB or severe atypical mycobacterial infection. He showed dramatic improvement after antimycobacterial therapy and the patient was discharged after 1 month of hospitalization on Isoniazide, Rifampicin and Pyrazinamide. Subsequently, chest X-ray normalized. But sputum smears still positive for AFB after 4 months of treatments. Within 5 months, most of patient symptoms disappeared and scrotal, Abdominal and neck U/S normalized and sputum smears for AFB became negative.

Discussion

SIgM deficiency is a rare form of dysgammaglobulinemia which was described first in 2 children with fulminant meningococcal septicemia, more than 45 years ago [1] and characterized by an isolated low level of serum immunoglobulin M (IgM). There have been a few cases reported in the literature, with a reported prevalence of 0.03–3% [2–4]. Adults with primary sIgM deficiency usually associated with autoimmune diseases and malignant neoplasm [3,4] whereas children may present with severe life-threatening infections, a few cases of possible primary sIgM deficiency in adults with no evidence of autoimmunity or malignant neoplasm have been reported [5]. Adult patients usually present with mild infections. Our patient, who was previously healthy with no evidence of autoimmunity or neoplasm, represents a possible case of primary sIgM deficiency in adults with severe life-threatening and unusual infections (Miliary tuberculosis). We reviewed and compared previously reported 43 patients with sIgMID from 1967 to 2015, including our patient, and their characteristics are summarized in Table 2.

IgM provides the initial response to foreign antigen and plays a regulatory role in the subsequent immune response development, accelerating the production of high-affinity IgG [6]. SIgM deficiency can be asymptomatic or may symptomatically present with infections from encapsulated bacteria and viruses, some of which can be serious and even life threatening infections varying from pneumonia to septicemia and meningitis. A few cases of sIgMD with mycobacterium avium complex (MAC) infection or *M. tuberculosis*, but none of them presented with MTB without T-cell disorders [7].

In primary sIgM deficiency, B cells, T cells and T cell subsets, and NK cells are normal [2,8]. T cell functions are normal [2]. Innate immune functions are normal [2]. Specific antibody response to pneumococci is impaired in 50% of symptomatic cases [2] as in our case. However, several patients with selective IgM deficiency and T cell and NK cell defects with MAC intracellulare infections have been reported [7]. In a subset of patients with sIgM deficiency circulating IgM + B cells are decreased or completely lacking. Specific IgG antibody responses against pneumococcus polysaccharides are impaired in a subset of patients with selective IgM deficiency who appear to respond to immunoglobulin therapy [6]. Furthermore, immunologic investigation neglected any possibility of an immune defect associated with tuberculosis, In our case the innate immunity is intact. T cells, T cell subsets, and T cell functions and phagocytic responses, serum IgA,

Table 1 – Laboratory findings on admission.

	Patient result	Reference range
White blood cell count, $10^3/\mu L$	8.8	4.0–10.5
Hemoglobin, g/dL	9.8	13.5–16.9
Platelets, $10^3/\mu L$	396	150–400
Absolute neutrophil count, $10^3/\mu L$	7.12	2.0–8.1
Absolute lymphocyte count, $10^3/\mu L$	0.88	0.9–3.3
Absolute monocyte count, $10^3/\mu L$	0.61	0.0–0.8
Absolute eosinophil count, $10^3/\mu L$	0.01	0.0–0.54
Purified protein derivative	Negative	Negative
Antistreptolysin-O IU/ml	Negative	Negative
ESR	70	5
Adaptive immunity		
Lymphocyte subsets, No./μL (%)		
CD3+ T cells	712 (81%)	619–1847 (62–84)
CD3+ CD4+ T cells	510 (58%)	338–1194 (31–61)
CD3+ CD8+ T cells	202 (23%)	85–729 (10–38)
Ratio of CD4/CD8	2.52	(0.9–3.7)
CD3-CD19 + B cells	123 (14%)	51–473 (5–26)
CD3-CD56 + NK cells	44 (5%)	12–349 (1–17)
Serum immunoglobulins		
IgM, mg/dL	17.4	65–263
IgA, mg/dL	305.7	68–378
IgE, mg/dL	24.5	10–150
IgG, mg/dL	1488	694–1618
Autoantibodies		
ANA	Negative	Negative
Anti-dsDNA antibody	Negative	Negative
ANCA	Negative	Negative
Lupus anticoagulant	Negative	Negative
RF	Negative	Negative
Innate immunity		
C3, mg/dL	96	88–201
C4, mg/dL	24	16–47
CH50 U/mL	235	101–300
Phagocytosis		
CD11b	95%	80–100
CD18	99%	80–100
Serological blood tests		
HIV 1,2 Ab, ELISA	Negative	Negative
HBs-Ag	Negative	Negative
HCV-Ab	Negative	Negative
Biochemistry		
Cr mg/dL	0.5	0.4–1.1
UA mg/dL	2.3	3.4–7
T-Bil mg/dL	0.41	0.2–1.1
ALB mg/dL	3.1	3.5–5
AST U/L	57	0–41
ALT U/L	48	0–41
LDH U/L	231	141–247

IgE, IgG, and IgG subclasses were normal. The presence of the BCG scar as well as normal lymphocyte blastogenesis ruled out SCID.

Several studies have previously reported and classified IgM deficiency in primary or secondary type. Our patient had no history of autoimmune disease or malignancy, as demonstrated in secondary IgM deficiency, so primary IgM deficiency was suggested. Is there any possibility of direct relationship between occurrence of secondary IgM deficiency and MTB? So, after 5 months of treatment with negative results of sputum smears for AFB, we reinvestigated the serum level of IgM, which was low (22 mg/dL) and serum IgG, IgA, and IgE were normal (1153, 233.2, 42 mg/dL respectively) with a normal lymphocyte count. After an extensive literature review, we found relationship between lymphopenia and MTB. Lymphopenia improved after starting antituberculosis treatment [9]. However, they could not come up with a direct relationship between the cause of IgM deficiency and tuberculosis.

Table 2 – Summary of reported cases with selective IgM deficiency.

	Age	Sex	Diagnosis	Presentation	Prognosis	Author	Year
1	8	M	Primary	Acute meningococcal septicaemia	Death	Hobbs et al. [1]	1967
2	13	M	Secondary	Autoimmune hemolytic anemia	Recovery	Stoelinga et al.	1969
3	18	M	Primary	Chronic meningococcemia	Death	Fass et al.	1972
4	65	M	Primary	Bloody diarrhoea	Recovery	Ross et al.	1976
5	72	M	Primary	Diarrhoea	Recovery	Ross et al.	1976
6	60	M	Primary	Pulmonary tuberculosis	Death	Ross et al.	1981
7	21	M	Primary	Smallpox	Recovery	Brilliant et al.	1981
8	41	F	Secondary	Clear cell sarcoma	Death	Vogelzang et al.	1982
9	47	M	Secondary	Prolymphocytic leukemia	Death	Takenaka et al.	1983
10	16	F	Primary	Disseminated molluscum contagiosum	Recovery	Mayumi et al.	1986
11	42	M	Primary	Pyelonephritis	Recovery	Inoue et al.	1986
12	48	M	Primary	Pneumonia	Recovery	Inoue et al.	1986
13	58	M	Primary	Urinary infection, tuberculos	Recovery	Inoue et al.	1986
14	71	F	Primary	Urinary infection, pneumonia	Recovery	Inoue et al.	1986
15	73	F	Primary	Urinary infection, bronchitis	Recovery	Inoue et al.	1986
16	50	F	Secondary	Systemic lupus erythematosus	Recovery	Saiki et al.	1987
17	50	M	Primary	Cholangitis, gout, liver abscess, dermatitis	Recovery	Yamasa et al.	1992
18	57	M	Primary	Diabetes mellitus	–	Yamasa et al.	1992
19	22	M	Primary	Streptococcal infection	Recovery	Yamasa et al.	1992
20	34	M	Primary	Psoriasis pustulosa, chronic tonsillitis, bronchitis pustulosa, bronchitis	Recovery	Yamasa et al.	1992
21	57	M	Primary	Diabetes mellitus, polyarthritis	Recovery	Yamasa et al.	1992
22	37	F	Primary	Asymptomatic	–	Yamasa et al.	1992
23	70	M	Secondary	Hashimoto's disease	Recovery	Kimura et al.	1993
24	25	F	Primary	Epidermodysplasia verruciformis	Recovery	Iraji et al.	2000
25	23	F	Secondary	Systemic lupus erythematosus	Recovery	Takeuchi et al.	2001
26	18	M	Secondary	Chronic idiopathic thrombocytic purpura	Recovery	Sugita et al.	2001
27	15	F	Primary	22q11.2 deletion syndrome chronic otitis media	Recovery	Kung et al.	2007
28	6	M	Primary	22q11.2 deletion syndrome chronic otitis media	Recovery	Kung et al.	2007
29	13	F	Primary	Recurrent otitis media	Recovery	Kung et al.	2007
30	57	M	Secondary	Autoimmune glomerulonephritis	Recovery	Antar et al.	2008
31	49	M	Primary	*Streptococcus pneumonia* sepsis and invasive aspergillosis	Recovery	Hong et al.	2008
32	47	M	Primary	Chronic recurrent multifocal osteomyelitis	Recovery	Makay et al.	2009
33	6.5	M	Primary	Recurrent impetigo	Recovery	Belgemen et al.	2009
34	13	M	Secondary	Anaplastic large cell lymphoma	Recovery	Saini et al.	2011
35	70	M	Primary	*Mycobacterium avium* intracellulare. pneumonia	Recovery	Gupta et al.	2000
36	56	F	Primary	*Mycobacterium avium* intracellulare. pneumonia	Death	Gupta et al.	2001
37	48	F	Primary	*Mycobacterium avium* intracellulare. pneumonia	Recovery	Gupta et al.	2012
38	42	M	Secondary	Celiac disease	Recovery	Eli Magen et al.	2012
39	37	M	Primary	*Streptococcus pneumoniae* septic arthritis	Recovery	Phuphuakrat et al.	2013
40	64	M	Secondary	Autoimmune liver cirrhosis with recurrent hepatocellular carcinoma	Death	Arahata et al.	2013
41	58	M	Primary	Recurrent pneumonia (TB)	Recovery	Varun et al.	2014
42	40	M	Primary	Terminal ileitis due to yersinia enterocolitica infection	Recovery	Spyropoulos	2015
43	31	M	Primary	Miliary tuberculosis	Recovery	Our case	2015

Gerasimos, et al. reported an HIV-seronegative adult with disseminated TB having marked T-lymphocytopenia, which normalized after treatment with anti-tuberculosis therapy. Lymphocytopenia was attributed to disseminated TB [10]. There is no obvious explanation for the cause of T cell depletion. Probabilities include consumption at the site of infection, such as the lungs or suppression of T cell production by the MTB. Certain components of MTB such as D-arabino-D-galactan activate suppressor mechanism in vitro, which in turn might cause lymphocyte depletion [10] and IgM deficiency as a part of immune system suppression. It may be the observation of a phenomenon that need to be supported by conducting a cohort study of patients with MTB by analyzing lymphocyte subsets and IgM deficiency in a prospective manner.

In contrast, the pathogenesis of primary sIgM deficiency is unknown with no specific genetic or molecular basis defined. A number of defects have been reported, including intrinsic B cell defects in plasma cell differentiation [8], increased T cell suppressor activity, which may be specific to IgM isotype or isotype-nonspecific [5]. There is no report of formation of anti-IgM antibodies (anti IgA occur in 20–40% of sIgA deficiency). Furthermore, transformation to panhypogammaglobulinemia or common variable immunodeficiency has not been reported for sIgMID, although subclass IgG deficiencies can occur [8]. This suggests that sIgM deficiency is a heterogeneous disorder, which requires further studies to elucidate the predominant mechanisms involved in its pathogenesis.

Although a role of antibodies in defense against MTB has not been described in detail, there is some evidence for the role of B cells and antibodies in host defense against intracellular pathogens including M. tuberculosis, as B cells can regulate both CD4+ and CD8+ T cell memory responses and produce antibodies and cytokines which can modulate the maturation of antigen-presenting cells. Also B cells can regulate the differentiation of macrophages into subsets which are important in anti-mycobacterial defense. While role of antibodies are evident in the presence of monoclonal antibodies specific for a number of mycobacterial components including arabinomannan, lipoarabinomannan, heparin-binding hemagglutinin, and 16kD-crystalin, and passive transfer of serum with polyclonal antibodies against M. tuberculosis is protective in relapse of tuberculosis in SCID mice and the role is also supported by M. tuberculosis infections in patients with X-linked agammaglobulinemia. Ultimately, a role of antibodies in mycobacterial defense is supported by the presence of IgG antibodies against glycopeptidolipid (GPL) core antigen of MAC in 77% of patients with pulmonary MAC and none in pulmonary tuberculosis [11]. Therefore, an antibody defect in our patient may be responsible for the development of MTB. Further examination using lymphocytes of the patient with sIgMD will be necessary to establish the pathogenesis of this disease.

Conclusion

Miliary tuberculosis without T-cell disorders in a healthy adult should lead to further investigation of underlying diseases including primary immunodeficiencies.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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