

A 45-year-old man with elevated levels of immunoglobulin A

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ABSTRACT

Quantitative immunoglobulin tests are often ordered as part of the initial evaluation for suspected immune deficiency. Although alterations in immunoglobulin levels can explain recurrent infections, in a patient without symptoms, there are a variety of other factors that can alter immunoglobulin levels. Common causes for elevated immunoglobulin A levels include malignancy and hepatic impairment in addition to a variety of infiltrative, infectious, and inflammatory diseases. We present a case of a 45-year-old man with a history of recurrent sinopulmonary symptoms without bacterial infection found to have an isolated elevated level of immunoglobulin A.

(Allergy Asthma Proc 39:394–397, 2018; doi: 10.2500/aap.2018.39.4161)

CHIEF CONCERN

Elevated immunoglobulin A (IgA) level.

HISTORY OF PRESENT ILLNESS

A 45-year-old man with a history of hypertension, dyslipidemia, and irritable bowel syndrome presented for an immunology consultation for elevated IgA obtained as part of an evaluation for recurrent sinopulmonary symptoms. The patient reported 10 sinopulmonary “infections” in the past 10 months, with frequent episodes of rhinorrhea that alternated with nasal congestion, sinus pressure, sore throat, and coughing. He had no history of nasal symptoms, polyps, or major infections. He never required antibiotic treatment because the symptoms self-resolved within 2 weeks. In the past month, his symptoms became more persistent, and he received a 10-day course of amoxicillin-clavulanate for suspected sinusitis, after which symptoms completely resolved. He did not have documented abnormal cultures or imaging. A review of systems was otherwise unremarkable. He did not have fevers, chills, night sweats, weight loss, jaundice, nausea, abdominal pain, joint pain, skin

changes, lymphadenopathy, or changes to bowel or bladder patterns.

He was not taking any prescription medications but started acupuncture 6 months earlier. He reported taking multiple herbal supplements and currently was taking Bone Broth Protein Turmeric (Ancient Nutrition LLC, North Palm Beach, FL), Garden of Life Super Seed (Certified B Corporations, Palm Beach Gardens, FL), Raw One Multivitamin (Certified B Corporations, Palm Beach Gardens, FL), Carlson Super Omega 3 (Carlson Laboratories Inc, Arlington Heights, IL), Syn-tol AMD probiotic (Arthur Andrew Medical, Scottsdale, AZ), Ecliptex (Health Concerns, Oakland, CA), and Ease 2 Chai Hu Gui Zhi Tang (Health Concerns, Oakland, CA). These supplements were frequently changed by his acupuncturist, depending on his symptoms. His family history was significant for myocardial infarction in his maternal grandmother at age 52 years old. He otherwise had no known family history of immunodeficiencies or autoimmune disease.

PHYSICAL EXAMINATION

Vital signs were within normal limits. He was well appearing and not obese. Results of his examination were remarkable only for bilateral inferior turbinate hypertrophy with boggy pale mucosa and clear mucous. Posterior oropharynx was clear without cobblestoning. Results of a cardiac examination revealed a regular rate and rhythm, and the absence of murmurs. The lungs were clear bilaterally. The abdomen was soft and nontender, with normoactive bowel sounds. There was no lymphadenopathy or significant hepatosplenomegaly. The extremities were not edematous.

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No external funding sources reported

The authors have no conflicts of interest to declare pertaining to this article

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LABORATORY FINDINGS

The patient had completed recent blood work as part of his annual physical examination. A complete blood cell count revealed no neutropenia (white blood count, 5530/ μ L), although he had a new mild anemia (hemoglobin, 11.8 g/dL) and thrombocytopenia (118,000/ μ L). His basic metabolic panel was normal, with a creatinine level of 0.66 mg/dL. He had hyperbilirubinemia (total bilirubin level, 2.3 mg/dL), with elevated transaminases (aspartate transaminase level, 175 U/L; alanine transaminase level, 87 U/L; alkaline phosphatase, 212 U/L). A fasting lipid panel revealed marked dyslipidemia (total cholesterol level, 1128 mg/dL; low density lipoprotein level, 827 mg/dL; high density lipoprotein level, 50 mg/dL; triglycerides, 395 mg/dL). He had an isolated elevated IgA level of 750 mg/dL (reference range, 87–426 mg/dL), with normal IgG (1220 mg/dL), IgM (265 mg/dL), and IgE (59 mg/dL) values. Previous laboratory studies (complete blood cell count, basic metabolic panel, and liver function tests) had been normal 7 months earlier. Three years ago, he had a normal IgA level of 368 mg/dL, obtained as part of the workup for celiac disease. At that time, he had normal laboratory study results, including liver function tests, although a fasting lipid panel showed mild dyslipidemia (total cholesterol level, 284 mg/dL; low density lipoprotein level, 174 mg/dL; high density lipoprotein level, 59 mg/dL; triglyceride level, 421 mg/day).

CLINICAL COURSE AND ADDITIONAL WORKUP

To address his history of primarily sinopulmonary symptoms, we initiated an empiric regimen of daily saline solution sinus rinses, followed by an intranasal corticosteroid spray. Sinus imaging was not obtained because the patient was asymptomatic at the time of evaluation. We discussed the role of testing for environmental sensitizations, but this was deferred because testing was unlikely to change acute management of his sinus disease. In assessing the patient's risk factors for hepatic disease, we learned he had a >20-year history of heavy alcohol use. In the past month, he had cut down from 27 drinks per week (3 glasses of wine daily, 6 drinks on the weekends) to ~10 drinks per week. He endorsed that he had been drinking heavily around the time of his physical examination and laboratory tests. He stated that he had no history of illicit or intravenous drug use or blood transfusions, although he had a homemade tattoo placed on his arm during his teenage years that had subsequently been removed.

Further laboratory studies showed that the patient did not have human immunodeficiency virus and total complement was normal. B-cell, T-cell, and natural-killer cell enumerations were normal. Serum protein electrophore-

sis and serum immunofixation did not show a monoclonal pattern. Results of a hepatitis panel were negative. Iron studies were not consistent with hemochromatosis. Dyslipidemia was confirmed by multiple assays, and, after consultation with a lipid specialist, the patient was diagnosed with familial hypercholesterolemia. To further characterize the liver pathology, abdominal ultrasound was obtained, which showed mild hepatomegaly with hepatic steatosis.

To evaluate for fibrosis, magnetic resonance imaging with elastography was obtained of the liver, which showed steatosis without evidence of fibrosis. After 2 weeks of abstaining from alcohol and discontinuing all herbal supplements, along with medical management of his dyslipidemia, results of the patient's liver function tests quickly normalized. Due to the patient's normal liver function tests 7 months earlier, the acute change in the setting of recent antibiotics and timing of starting herbal supplements, the patient was thought to have drug-induced liver inflammation on a background of hepatic steatosis from long-term alcohol use and metabolic syndrome. No further hepatic workup, therefore, was pursued. At his follow-up visit 2 months later, the patient had not experienced any interim major infections. His sinus symptoms were well controlled. We planned to recheck his IgA level; however, we learned that he had experienced several interim relapses of alcohol use and his liver transaminase levels were elevated again. He, unfortunately, was lost to immunology follow up thereafter.

DISCUSSION

Immunoglobulins function to combine with and facilitate removal of foreign antigens from the body. Human IgA is one of these antibodies, predominantly found in its monomeric form in the serum and polymeric form in secretions.¹ IgA is known to be important in neutralizing bacteria and viruses by interfering with epithelial adhesion and removing antigens at sites with mucosal linings (mouth, digestive tract, and respiratory tract). Typically, recurrent sinopulmonary infections are associated with immunoglobulin deficiency, although numerous abnormalities of immunoglobulin production can occur. There can be either congenital or acquired deficiencies of one or all of the immunoglobulins, and, conversely, there can also be an overproduction of any immunoglobulin.² When considering if a level is abnormal, one should interpret the result by using reference ranges based on age-matched controls. Immunoglobulin levels change with age, with minor differences detected based on sex and race. Total serum IgA has been shown to be positively associated with increased age, male sex, heavy alcohol use, and the presence of metabolic syndrome.³ The incidence of an isolated elevated IgA level is unknown.

Table 1 Differential diagnoses of elevated immunoglobulin A (IgA) levels

Monoclonal IgA
Systemic amyloidosis
Multiple myeloma
Monoclonal gammopathy of undetermined significance
Solitary plasmacytoma
Polyclonal IgA
Infection
IgA nephropathy
Wiskott Aldrich syndrome
Intestinal inflammatory disease
Connective tissue disease
Rheumatoid arthritis
Systemic lupus erythematosus
Mixed connective tissue disorder
Vasculitis
Liver disease
Cirrhosis
Hepatitis
Biliary disease
Steatosis

Increased serum immunoglobulin levels can be either monoclonal or polyclonal (Table 1). If our patient had a high IgA level with monoclonal gammopathy, then the differential diagnosis would include multiple myeloma, monoclonal gammopathy of undetermined significance, and primary systemic amyloidosis. Our patient had a polyclonal elevation of IgA, which is usually associated with underlying infectious or inflammatory processes.⁴ The most common etiology for polyclonal gammopathy is liver disease, but also includes intestinal inflammatory disease, connective tissue disease, and acute and chronic infections.⁵ Given the role of IgA, it is often elevated with infections that cause mucosal antigenic stimulation,¹ with one case report of an elevated IgA value in a young patient with chronic salmonellosis.⁶ Gammopathies can also cause tissue deposition, such as IgA nephropathy.¹

Very high concentrations of total IgA have especially been found in patients with chronic liver disease.¹ High levels of IgA are found in patients with hepatitis and cirrhosis, independent of alcoholic or nonalcoholic etiologies. Patients with milder disease, such as steatosis and fibrosis from alcohol use, had much higher IgA concentrations compared with those with nonalcoholic liver disease.⁷ It has also been proposed that increased bacterial overgrowth and gut translocation in patients with chronic liver disease, especially those with cirrhosis, cause B cells to activate and overproduce immunoglobulins, *e.g.*, IgA.^{8,9} In addition, patients with chronic

liver disease have alterations in IgA receptors, which reduce IgA clearance and catabolism.^{1,10}

FINAL DIAGNOSIS

Elevated IgA levels that corresponded with acute liver inflammation from multifactorial drug-induced liver injury.

CONCLUSION

Our patient had recurrent sinopulmonary symptoms that did not require antibiotic treatment, without documented culture or imaging suggestive of infection. We had a higher suspicion for untreated chronic rhinitis causing recurrent sinopulmonary symptoms rather than true immune deficiency. With empiric treatment, the patient's symptoms were well controlled. The incidental finding of an elevated IgA level, however, highlighted an interesting differential diagnosis in a patient who had multiple risk factors known to be correlated with an elevated IgA level. Interestingly, none of these risk factors corresponded with an elevated IgA level just 3 years earlier. The newly elevated IgA level seemed to correspond with acute hepatic inflammation as shown by elevated liver transaminase levels, which were thought to be due to a combination of herbal supplements, antibiotics and alcohol causing multifactorial drug-induced liver injury. Ultimately, we would have liked to repeat an IgA level assessment at the time of normal liver function tests to see if the IgA level correspondingly normalized; however, we were unable to do so due to interim alcohol relapses and the loss to follow up.

REFERENCES

1. Delacroix DL, Elkom KB, Geubel AP, Hodgson HF, Dive C, and Vaerman JP. Changes in size, subclass, and metabolic properties of serum immunoglobulin A in liver diseases and in other diseases with high serum immunoglobulin A. *J Clin Invest.* 1983; 71:358–367.
2. Williams RC, and Gibbons RJ. Inhibition of bacterial adherence by secretory immunoglobulin A: a mechanism of antigen disposal. *Science.* 1972; 177:697–699.
3. Gonzalez-Quintela A, Alende R, Gude F, et al. Serum levels of immunoglobulins (IgG, IgA, IgM) in a general adult population and their relationship with alcohol consumption, smoking and common metabolic abnormalities *Clin Exp Immunol.* 2008; 151: 42–50.
4. Wilson DA, Walker HK, Hall WD, et al. *Immunologic Tests. Clinical Methods: The History, Physical, and Laboratory Examinations.* 3rd ed. Boston, MA: Butterworths; 1990.
5. Dispenzieri A, Gertz MA, Therneau TM, et al. Retrospective cohort study of 148 patients with polyclonal gammopathy. *Mayo Clin Proc.* 2001; 76:476–487.
6. Stites DP, Levin AS, Lauer BA, Costom BH, and Fudenberg HH. Selective “dysgammaglobulinemia” with elevated serum IgA levels and chronic salmonellosis. *Am J Med.* 1973; 54:260–264.
7. van de Wiel A, van Hattum J, Schuurman HJ, and Kater L. Immunoglobulin A in the diagnosis of alcoholic liver disease. *Gastroenterology.* 1988; 94:457–462.

8. Massonnet B, Delwail A, Ayrault JM, Chagneau-Derode C, Lecron JC, and Silvain C. Increased immunoglobulin A in alcoholic liver cirrhosis: exploring the response of B cells to Toll-like receptor 9 activation. *Clin Exp Immunol.* 2009; 158:115–124.
9. Van de Wiel A, Seifert WF, Van Der Linden JA, Gmelig-Meyling FH, Kater L, and Schuurman HJ. Spontaneous IgA synthesis by blood mononuclear cells in alcoholic liver disease. *Scand J Immunol.* 1987; 25:181–187.
10. Silvain C, Patry C, Launay P, Lehuen A, and Monteiro RC. Altered expression of monocyte IgA Fc receptors is associated with defective endocytosis in patients with alcoholic cirrhosis. Potential role for IFN-gamma. *J Immunol.* 1995; 155:1606–1618. □

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