CASE REPORT

Novel variant of common variable immunodeficiency

Eileen Conaway^{1,2}

¹Graduate Medical Education,
Florida Hospital East Orlando,
Orlando, Florida, USA

²Nova Southeastern University,
Fort Lauderdale, Florida, USA

Correspondence to

Dr Eileen Conaway,
econawaydo@gmail.com

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SUMMARY

A 57-year-old woman with frequent respiratory infections was initially diagnosed with IgG subclass deficiency based on low levels of IgG subclasses 2 and 3. Three years later, she progressed to having IgA deficiency as well. With a normal total IgG level, she does not meet criteria for common variable immunodeficiency (CVID). This may represent a variant of CVID. This also highlights the importance of immunoglobulin subclass estimation in patients where immunodeficiency is suspected clinically. She is being treated with rotational antibiotics the first 10 days of every month, monthly intravenous immunoglobulin (IVIg) infusion and osteopathic manipulation one to two times per month. On this regimen, although she has had several viral respiratory infections, she has avoided further hospitalisation for more than 1 year.

BACKGROUND

A 57-year-old woman with frequent respiratory infections was found to have IgG subclass 2 and 3 deficiencies and then later developed IgA deficiency. This combination is here to date not described in the literature and may represent a novel form of common variable immunodeficiency (CVID). As there are no previous reports of this specific immunodeficiency, treatment strategy had to be extrapolated from separate IgG subclass deficiency, CVID and IgA deficiency treatment recommendations.

CASE PRESENTATION

The patient is a 57-year-old woman who was hospitalised four times in a 9-month period with pneumonia (table 1). On the third hospitalisation, *Streptococcus pneumoniae* was identified as the cause. This prompted a more extensive immune work-up as the patient had been previously vaccinated with the 23-valent pneumococcal polysaccharide vaccine. At that time, she was found to have IgG subclass 2 and IgG subclass 3 deficiencies (table 2). Total IgG, other IgG subclasses, IgM and IgE were all within normal limits. Total IgA was low, but still within the normal limits. A vaccine challenge with the 23-valent pneumococcal polysaccharide vaccine was attempted and upon failing to mount an IgG response, she was deemed a non-responder (table 3). She was started on weekly subcutaneous IgG replacement therapy. While on therapy, she was vaccinated with pneumococcal conjugate, 23-valent pneumococcal polysaccharide, and tetanus-diphtheria-pertussis vaccines and had a measurable IgG vaccine response (table 3). She remained on subcutaneous

IgG replacement therapy for the next 2 years and had only a single episode of pneumonia in both 2014 and 2015. In November 2015, she was transitioned to a different subcutaneous IgG product infused monthly for convenience of dosing. A short time later, she had two separate episodes of pneumonia. She was also noted to have a large subcutaneous fluid collection in her abdominal region and it was suspected that she was not absorbing the IgG product. Post infusion laboratory studies confirmed no IgG response to therapy. The patient then began monthly intravenous immunoglobulin (IVIg) replacement. Due to side effects of headache, malaise and myalgia, she elected to stop therapy from May to June 2016 at which time her immunoglobulins were measured again. She was now found to have an IgA deficiency in addition to the previously noted IgG subclass 2 and subclass 3 deficiencies. She was started on IVIg 10% at a 0.4 mg/kg dose¹ to address the IgG subclass deficiency as well as rotational antibiotics for prophylaxis for the IgA deficiency. For the first 10 days of each month, she takes on a rotational basis: ciprofloxacin 500 mg twice daily, sulfamethoxazole-trimethoprim 800/160 mg twice daily or amoxicillin-clavulanate 875/125 mg twice daily.

DIFFERENTIAL DIAGNOSIS

1. IgG subclass deficiency
2. IgA with IgG subclass deficiency
3. Wiskott-Aldrich syndrome
4. agammaglobulinaemia.

This patient's initial diagnosis was IgG subclass deficiency as she met diagnostic criteria with a normal IgG level, but reductions in IgG subclasses 2 and 3. However, three years later she demonstrated IgA deficiency as well, which is not a feature of IgG subclass deficiency.

IgA with IgG subclass deficiency is unlikely as the patient initially had a normal level of IgA when she first became symptomatic.² It is plausible that there are other patients like this one who are classified as IgA with IgG subclass deficiency, but who would have had normal IgA levels and only IgG subclass deficiency measured in the years before their diagnosis was made.

Wiskott-Aldrich syndrome, another major primary immunodeficiency, features increased susceptibility to infections and inflammatory skin conditions due to dysfunctional immune system as well as clotting disorder due to microthrombocytopenia.³ This condition is rare in women and otherwise not a viable differential diagnosis for this patient as she does not exhibit any signs or laboratory studies suggestive of clotting disorder.

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Table 1 Timetable and pathogen of pneumonia hospitalisations

Month	Pathogen	Method of pathogen identification
October 2012	No pathogen isolated	
January 2013	Parainfluenza virus	Nasopharyngeal secretion DFA
March 2013	<i>Streptococcus pneumoniae</i>	Urine antigen
June 2013	<i>Haemophilus influenzae</i>	Sputum culture
February 2014	Parainfluenza virus 4	Nasopharyngeal secretion PCR
April 2015	<i>Moraxella catarrhalis</i>	Sputum culture
January 2016	<i>Streptococcus viridans</i>	Bronchoalveolar lavage culture
February 2016	<i>Rhinovirus/Enterovirus</i>	Nasopharyngeal secretion PCR

DFA, direct fluorescent antibody.

Agammaglobulinaemia is usually only symptomatic in men as it is an X-linked genetic disorder.⁴ Additionally, symptoms usually appear very early in childhood due to overall suppression of all immunoglobulins.

TREATMENT

Current treatment is threefold and includes: IVIG 10% at a 0.4 mg/kg dose, rotational antibiotics for the first 10 days of each month including ciprofloxacin 500mg twice daily, sulfamethoxazole-trimethoprim 800/160mg twice daily, or amoxicillin-clavulanate 875/125 mg twice daily, and osteopathic manipulation.

OUTCOME AND FOLLOW-UP

The patient has continued to contract viral respiratory infections; however, she has avoided hospitalisation for more than 1 year. She continues to be seen in the outpatient office approximately once per month.

DISCUSSION

IgG composes approximately 75%–85% of the total human serum immunoglobulin, and the portion comprised by each subclass descends with IgG1 being the most and IgG4 the least.⁵ IgG2 primarily makes antibodies to polysaccharides of encapsulated bacteria such as *S. pneumoniae*, *Neisseria meningitidis*, *Klebsiella pneumoniae* and *Haemophilus influenzae* B.⁶ IgG3 antibodies target viral proteins as well as toxins produced by some bacteria such as *Corynebacterium diphtheriae* and *Clostridium tetani*.⁶ IgA composes approximately 7%–15% of the total human serum immunoglobulin, but is prevalent in secretions.⁵ IgA functions in the alternative complement pathway and can prevent viruses from binding to respiratory and gastrointestinal

epithelium.⁵ The different pathogens isolated in this patient's infections are readily explained by the specific identified immunoglobulin deficiencies and serve as a diagnostic clue as to the suggested immunodeficiency.

This case highlights the need for diligent thorough work-up of patients with recurrent infections suggestive of immunodeficiency. During initial work-up if IgG subclass analysis had not been performed, diagnosis of immunodeficiency would have been further delayed given the normal total IgG level. It is also possible that had IgA subclass analysis been completed at that time, that one of the subclasses may have been deficient given the initial low total IgA. Therefore, if CVID or other primary immunodeficiency is suspected based on clinical presentation, a full panel of immunoglobulins and subclass analysis should be performed so as not to overlook patients who do not meet strict diagnostic criteria, yet clearly have significant immune dysfunction.

Several years after initial diagnosis of IgG subclass deficiency, this patient displayed a progression of immunodeficiency to include total IgA and both IgA subclass deficiencies. Additionally, although they do not fall below the lower limit of normal, IgM and IgG subclass 4 are also markedly reduced. A comprehensive 40-year literature search using PubMed, Ovid, Clinical Key, Cochran and Google Scholar did not identify any similar previous reports.

The European Society of Immune Deficiencies' diagnostic criteria for CVID include: 'marked decrease of IgG (at least 2 SD below the mean for age) and a marked decrease in at least one of the isotypes IgM or IgA, and fulfills all of the following criteria 1) Onset of immunodeficiency at greater than 2 years of age, 2) Absent isohemagglutinins and/or poor response to vaccines; 3) Defined causes of hypogammaglobinemia have been excluded.'⁷ This patient matches the typical clinical course of CVID with onset later in life and diagnosis after several episodes of pneumonia.⁸ However, she does not fully meet the diagnostic criteria of CVID as she does not demonstrate a reduction of total IgG, but only IgG subclass deficiencies. Ameratunga *et al*⁷ put forward new more inclusive diagnostic criteria for CVID that would still exclude this patient from CVID diagnosis. Therefore, it is proposed that this patient represents a previously undescribed variant of CVID. Diagnostic criteria for this CVID variant would allow for the required marked decrease of IgG to be expanded to include deficiency of an IgG subclass. The other criteria of a decrease in an IgM or IgA isotype and the additional three minor features would remain.

The patient continues to receive monthly IVIG to address the IgG subclass deficiency component of her illness. The rotational

Table 2 Serum immune globulin laboratory results

	Reference range (mg/dL)	Values in 2013 at time of initial diagnosis (mg/dL)	Values in 2013 on IgG replacement (mg/dL)	Values in 2016 off IgG replacement therapy (mg/dL)
Total IgG	700–1600	837	1161	1120
IgG subclass 1	240–1118	629	880	760
IgG subclass 2	124–549	60 (low)	160	70 (low)
IgG subclass 3	21–134	8 (low)	10 (low)	3 (low)
IgG subclass 4	7–89	9	19	7
IgM	40–230	118		50
IgE	2–25	6		
IgA	70–400	73		40 (low)
IgA subclass 1	46–378			41 (low)
IgA subclass 2	13–91			9 (low)
Anti-IgA antibodies				Negative

Table 3 23-Valent pneumococcal polysaccharide vaccine challenge laboratory results

Serum immunoglobulin	Baseline (mcg/L)	Four weeks post vaccine (mcg/L)	Response rate	Six months of IgG replacement, 4 weeks post revaccination (mcg/L)	Response rate
Pneumococcal IgG 1	0.11	0.37	3.4	1.59	14.5
Pneumococcal IgG 3	0.06	0.26	4.3	1.29	21.5
Pneumococcal IgG 4	0.08	0.13	1.6	0.31	3.9
Pneumococcal IgG 5	1.16	10.06	8.7	5.37	4.6
Pneumococcal IgG 6b	0.38	0.50	1.3	1.71	4.5
Pneumococcal IgG 7f	0.45	2.53	5.6	2.67	5.9
Pneumococcal IgG 8	0.50	1.75	3.5	1.82	3.64
Pneumococcal IgG 9n	0.46	0.53	1.2	0.86	1.8
Pneumococcal IgG 9v	0.45	1.43	3.2	3.87	8.6
Pneumococcal IgG 12f	0.24	0.52	2.2	1.22	5.1
Pneumococcal IgG 14	2.44	2.76	1.3	3.77	1.5
Pneumococcal IgG 18c	1.89	3.15	1.7	4.33	2.3
Pneumococcal IgG 19f	0.22	0.67	3.0	3.04	13.8
Pneumococcal IgG 23f	0.83	1.52	1.8	1.07	1.3

A ratio of less than twofold is considered a non-responder.

A ratio of twofold to fourfold is a weak responder.

A ratio of fourfold or greater is a good responder.

antibiotics serve as prophylaxis due to her IgA deficiency. Osteopathic manipulation is also regularly performed on the patient. While osteopathic manipulation is generally more recognised outside the osteopathic community as a treatment for musculoskeletal manifestations, its use in systemic and infectious diseases dates back to its origin. During the 1918 influenza pandemic, the mortality rate in US hospitals was 30%–40%, the morality rate for patients treated by osteopathic physicians was 0.25%.⁹ This dramatic difference was due to the inclusion of osteopathic manipulation in the treatment plan. More recent randomised controlled studies demonstrate a statistically significant shorter length of stay and decreased intravenous antibiotic use in

patients hospitalised with pneumonia when osteopathic manipulation was used as an adjunctive therapy.¹⁰

Contributors EC is the sole author.

Competing interests None declared.

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Learning points

- Common variable immunodeficiency (CVID) may have variants not previously described.
- If CVID or other primary immunodeficiency is suspected based on clinical presentation, a full panel of immunoglobulins with subclass analysis should be performed.
- The trend towards defined diagnostic criteria is helpful for disease classification and treatment recommendations, but the art of medicine remains in how to use that data when a patient does not fit into a classification box.
- Increased reporting of cases such as this can aid the worldwide medical community in collaborating in the management of patients with atypical presentations or findings of known diseases.

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