Common Variable Immunodeficiency with C4 Deficiency

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ABSTRACT

Patients with common variable immunodeficiency (CVID) exhibit a high incidence of complement component 4A (C4A) gene deletions, however due to the presence of both C4A and C4B genes, C4 deficiency has not been seen in conjunction with CVID. The patient described herein was found to have both CVID and C4 deficiency, clinically presenting with a late-onset, severe palindromic rheumatism followed by infections.

Unique Aspect: This is the first report of C4 deficiency presenting concurrently in a patient with CVID.

INTRODUCTION

CVID is characterized by failure of B cell differentiation and impaired immunoglobulin production. Most cases are marked by recurrent respiratory tract bacterial infections, but CVID patients are also prone to lymphoproliferative disorders as well as inflammatory and autoimmune disease – 25% of cases occur with coexisting autoimmune phenomenon. Other derangements of the immune system, such as C2 deficiency, have been reported with CVID, however they are exceedingly rare.

CASE SUMMARY

- 67 year old male
- Persistent diffuse lymphadenopathy, chronic sputum production, & intermittent arthralgia, myalgia, ecchymosis, fatigue, malaise, anorexia, maculopapular rash for 2 years
- Multiple rounds of high-dose steroids; eventual symptomatic control on low-dose, daily prednisone
- Bone marrow, lymph node, & skin biopsies non-diagnostic
- Initial labs: elevated CRP, mildly low IgG, otherwise unremarkable
- 2 years later: panhypogammaglobulinemia, absence of humoral response to pneumococcal vaccination & near absence of memory B cells; C4 absent
- Subsequently developed persistent herpes zoster infection & recurrent sinusitis
- Started on IVIG therapy
- C4 genotyping is underway – results pending.

RESULTS

Table 1, Laboratory Values

	Reference Range	2013	2015
IgG (mg/dL)	700-1600	554	349
IgA (mg/dL)	70-400		47
IgM (mg/dL)	40-230		30
CD19+ cells	23-40%		0.6%
CH50 (U/mL)	30-75		3
C4 (mg/dL)	10-40		<2
C3 (mg/dL)	90-180		71
CD19+CD27+IGD (Naïve B Cells, %CD19)	(58-72.1)		81.4
CD19+CD27+IGD (Non-Switched Memory B Cells, %CD19)	(13.4-21.4)		0.3
CD19+CD27+IGD (Switched Memory B Cells, %CD19)	(9.2-18.9)		0.3

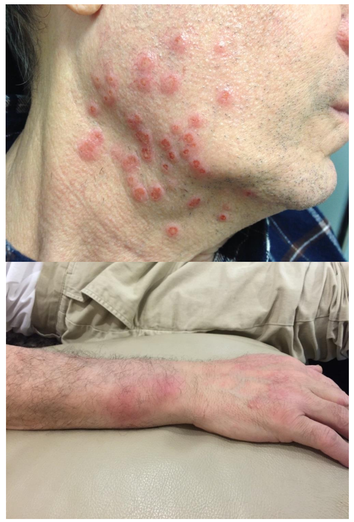

Figure 1: Herpes Zoster infection after weaning oral steroids

Figure 2: Unexplained ecchymosis

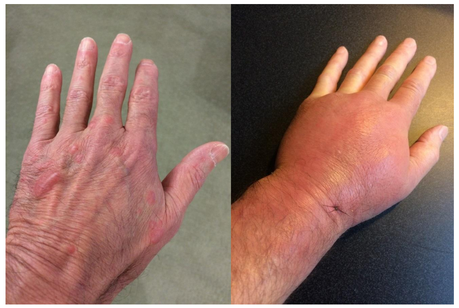

Figure 3: Maculopapular rash **Figure 4**: Hand edema

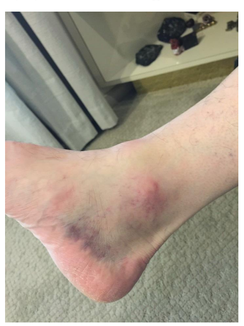

Figure 5: Unexplained ecchymosis

DISCUSSION

CVID has a strong association with autoimmune phenomenon, lymphoproliferation and increased infection risk. C4 is essential for the activation of the classical and mannose-binding lectin complement pathways playing a vital role in the integrity of innate and adaptive immune responses. The patient described was found to have both CVID and C4 deficiency with a infectious history worsening in adulthood, and a constellation of severe inflammatory symptoms for most of his life.

Deficiencies of complement in association with CVID have been reported, but full C4 deficiency has never been documented in association with CVID. Coexistence of C4 deficiency and hypogammaglobulinemia has been reported, specifically in SIgAD which is known to occasionally precede the development of CVID in certain individuals.

Interestingly, complement deficiencies involving the classical pathway have been recognized as one of the strongest genetic risk factors for SLE, with deficiencies of C4 specifically being linked with a variety of autoimmune phenomenon. It is possible that the overlay of patients with CVID and autoimmune phenomenon are deficient in C4 as well and may be at higher risk of developing infection, however this has not been formally evaluated.

CONCLUSIONS

- CVID is the most common PID, while C4 deficiency is exceedingly rare.
- C2 deficiency has been described in CVID patients, while C4 deficiency has been reported in hypogammaglobulinemia.
- C4 deficiency has been linked to autoimmune disease.
- An association between C4 deficiency and CVID has never been documented.
- Here we describe the first known case of CVID with C4 deficiency and palindromic rheumatism.