CASE REPORT

Unusual association between erythema nodosum and autoimmune atrophic gastritis

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SUMMARY

We report a case of a 46-year-old woman with a history of autoimmune atrophic gastritis and recurrent erythema nodosum (EN). Laboratory results showed iron-deficiency anaemia, positive antiparietal cell antibodies and marginal deficiency of vitamin B12. Although EN was refractory to general measures (rest and non-steroidal anti-inflammatory drugs) and corticosteroid therapy, it was successfully treated with vitamin B12 supplementation.

BACKGROUND

Erythema nodosum (EN) is a delayed type hypersensitivity reaction that usually affects women aged 20–40 years.¹ It typically presents with a sudden onset of tender, red/purple, nodular subcutaneous lesions, most frequently appearing on the anterior aspect of the legs, which may be associated with a variety of conditions or medications. It is generally a self-limited condition, resolving in a few months.

The pathophysiology of EN is still poorly understood and its association with atrophic gastritis (AG) and/or vitamin B12 (cobalamin) deficiency is scarcely reported in the literature.

This case alerts clinicians and the scientific community to a possible association between AG and EN, thus leading to a potential role for vitamin B12 supplementation as therapy of the latter.

CASE PRESENTATION

A 46-year-old woman presented with a 15-year history of generalised polyarthralgia, morning

stiffness of short duration (15–20 min), acrocyanosis, sicca symptoms, fatigue and recurrent episodes of painful erythematous lesions in her legs. She had a history of epilepsy, iron-deficiency anaemia and autoimmune atrophic gastritis, for which she was treated with valproic acid and oral/intravenous iron. Her family and epidemiological background were unremarkable, except an aunt who had systemic lupus erythematosus. On physical examination, she had multiple raised and tender purplish skin lesions (about 2–4 cm) in the anterior aspect of both legs, suggestive of EN (figure 1), with no other relevant findings.

DIFFERENTIAL DIAGNOSIS

Taking into account the aforementioned patient's history, the proposed main differential diagnoses were sarcoidosis, lymphoma, autoimmune condition (inflammatory bowel disease, coeliac disease, Behçet's disease, connective tissue disease) or infection. The most common associated conditions with EN are listed in box 1.^{1–4}

INVESTIGATIONS

Laboratory results showed microcytic hypochromic anaemia with iron deficiency (haemoglobin 9.2 g/dL (12.0–15.0), mean corpuscular volume 62.5 fL (83.0–101.0), mean corpuscular haemoglobin 18.9 pg (27.0–32.0), ferritin 6 ng/mL (10–120), iron 22 µg/dL (60–180), transferrin saturation 6% (20–40)) and positive antiparietal cell antibodies. Vitamin B12 levels (204 pmol/L) were in the lower laboratory reference values of our hospital

Figure 1 Lesions of erythema nodosum in the anterior aspect of the legs.

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Box 1 Most common conditions associated with erythema nodosum^{1–4}**Infections**

- ▶ Bacterial
 - *Streptococcus* spp (most common).
 - *Mycobacterium tuberculosis*.
 - *Yersinia enterocolitica*.
 - *Salmonella* spp.
 - *Campylobacter* spp.
 - *Mycoplasma pneumoniae*.
 - *Lymphogranuloma venereum*.
 - Brucellosis.
 - *Chlamydia trachomatis*.
- ▶ Viral
 - Epstein-Barr.
 - Cytomegalovirus.
 - Hepatitis.
 - HIV.
 - Herpes simplex.
- ▶ Fungal
 - Coccidioidomycosis.
 - Histoplasmosis.
 - Blastomycosis.
- ▶ Protozoal
 - Toxoplasmosis.
 - Giardiasis.
 - Amoebiasis.

Drugs

- ▶ Antibiotics.
- ▶ Oral contraceptives.
- ▶ Bromides and iodides.

Malignancy

- ▶ Haematological.
- ▶ Solid carcinoma.

Autoimmune/inflammatory conditions

- ▶ Inflammatory bowel disease.
- ▶ Connective tissue disease.
- ▶ Rheumatoid arthritis.
- ▶ Sarcoidosis.
- ▶ Vasculitis.
- ▶ Sweet syndrome.
- ▶ Coeliac disease.

Others

- ▶ Pregnancy.
- ▶ Whipple disease.
- ▶ Radiotherapy.
- ▶ Idiopathic.

(156–672 pmol/L)—marginal deficiency. The acute-phase reactants (C-reactive protein and erythrocyte sedimentation rate), remaining autoimmunity (intrinsic factor antibodies, antinuclear antibodies, antiextractable nuclear antigens, rheumatoid factor, anticyclic citrullinated peptide antibodies, antitransglutaminase antibodies, antigliadin antibodies, atypical antineutrophil cytoplasmic antibodies and anti-*Saccharomyces cerevisiae* antibodies), human leucocyte antigen (HLA)-B27 and HLA B-51 were negative, while total serum IgA, serum angiotensin converting enzyme, folic acid, complement, thyroid hormones,

serum protein electrophoresis, coagulation, renal and liver function were all within the normal range.

Bone X-rays, musculoskeletal ultrasound, capillaroscopy, colonoscopy and abdominopelvic ultrasound revealed no significant changes.

Chest X-ray and CT scan showed mild subpleural micronodular lesions, and the gallium scintigraphy presented mild hypercapitation of the parotid glands. In this context, a bronchoalveolar lavage fluid was performed which revealed a CD4/CD8 ratio of 2.21, 6% lymphocytes and negative cultures (including for mycobacteria). Lung and salivary gland (minor and parotid) biopsies and pulmonary function tests were unremarkable.

Upper endoscopy with gastric body and fundus as well as duodenal biopsy were also made, revealing glandular atrophy plus moderate intestinal metaplasia and a moderate mononuclear infiltrate of the lamina propria with mild activity, confirming the diagnosis of AG and excluding the hypothesis of coeliac disease or *Helicobacter pylori* infection.

TREATMENT

Initial therapies for EN, with rest and non-steroidal anti-inflammatory drugs (NSAIDs), in addition to iron replacement, were implemented with just a mild and temporary improvement regarding clinical manifestations as well as haemoglobin levels. Due to the maintenance of EN, short courses of corticosteroid therapy were started with a favourable clinical improvement, although during its tapering these lesions reappeared.

Even though determination of serum homocysteine and methylmalonic acid are suggested in the case of borderline/normal values of vitamin B12 to aid in the ascertainment of its underlying deficiency,^{5 6} we decided not to request it and start an immediate therapeutic trial of oral vitamin B12 supplementation (2000 µg/day).^{5 7 8} Our choice was supported by the presence of autoimmune AG and sideropenic anaemia as well as the report of two similar cases in the literature.^{9 10}

OUTCOME AND FOLLOW-UP

In the follow-up visit of this patient, a few weeks later, the lesions of EN had disappeared, and an improvement in the values of haemoglobin (13.5 g/dL) was also seen. The patient currently maintains a follow-up at the Rheumatology clinic, remaining stable without new lesions for more than 12 months.

DISCUSSION

Autoimmune AG results from immunological destruction of gastric parietal cells and is characterised by achlorhydria and loss of intrinsic factor, which are necessary for the intestinal absorption of vitamin B12 in the terminal ileum. This condition may, therefore, present with pernicious anaemia (PA), a type of megaloblastic anaemia.¹¹

Furthermore, AG may also be associated with impaired iron absorption due to raised gastric pH.¹² The resulting iron deficiency is usually clinically apparent before vitamin B12 deficiency.^{8 13} Hence, a microcytic anaemia may arise rather than the typical megaloblastic anaemia, as was apparent in this case report.

The determination of serum cobalamin can be misleading, especially for values around the lower limit of normal. The possible association of PA with spuriously normal-high vitamin B12 levels has been reported in the literature, and a potential explanation relates to the interference of high titers of intrinsic factor antibodies.^{13–15} Likewise, besides the normal range of vitamin B12 levels vary accordingly to different laboratories, it

Table 1 Reported cases of successful treatment of erythema nodosum with vitamin B12

Reference	Age	Gender	Management	Vitamin B12 levels	Associated conditions
Volkov <i>et al</i> ⁹	38 years	Female	1. NSAIDs 2. Vitamin B12 (intramuscular) 1 g 2×/week	118 pg/mL (135–911)	Peripheral neuropathy
Milman <i>et al</i> ¹⁰	34 years	Female	1. General measures 2. NSAIDs 3. Corticosteroids 4. Vitamin B12 (parenteral) dosage N/A	147 pg/mL (200–1100)	Autoimmune atrophic gastritis (fundus and body)+positive anti-intrinsic factor and antiparietal cell antibodies—pernicious anaemia

NSAIDs, non-steroidal anti-inflammatory drugs.

has also been stated that serum cut-off values widely ranged for deficiency of cobalamin.^{8 16} Therefore, a diagnosis of PA could not be excluded in our patient.

PA is treated with cyanocobalamin or hydroxocobalamin. Nevertheless, treatment regimens (route, dosage and schedule of administration) vary widely between healthcare institutions and doctors.⁵ Lifelong vitamin B12 supplementation is warranted. Effective treatment corrects blood counts in 8–12 weeks and may improve clinical manifestations within 3 months.^{17 18}

In the setting of AG with achlorhydria or hypochlorhydria, abnormal bacterial overgrowth often occurs.^{19–22} Milman *et al* have proposed that given the presence of mucosal damage coupled with abnormal bacterial proliferation in AG, the escape of bacterial antigen into the systemic circulation was likely.¹⁰ These bacterial antigens could then incite the development of EN,²³ which is considered a delayed-type hypersensitivity reaction. In its early stages, immune complex deposition in the septal venules of the subcutaneous fat, inflammatory cells recruitment, tumour necrosis factor- α production and granuloma formation appear to play a role as the cause of septal panniculitis.^{13 24} Nevertheless, evidence of this pathophysiological process remains elusive.

EN is usually a self-limiting condition and its treatment should be directed at the associated underlying condition and symptomatic relief. Aspirin, NSAIDs and potassium iodide may be helpful, although in refractory cases, systemic corticosteroids or other immunotherapy drugs may be used.

In the literature, two cases are reported regarding the improvement of EN after therapy with vitamin B12.^{9 10} In both patients, a mild deficiency of this vitamin was identified, even though only one of them also had a diagnosis of PA. The treatment consisted of parenteral vitamin B12 with favourable clinical and analytical outcomes (table 1).

In recent years, increasingly awareness has appeared regarding many medical conditions associated with vitamin B12 deficiency, including demyelinating diseases, psychiatric disturbances, haematological conditions and intrauterine developmental restrictions.

Some studies have demonstrated immunomodulatory effects and restoration of the immunological abnormalities with exogenous administration of cyanocobalamin to patients with PA: increase in the number of CD8 cells (thus normalising the CD4/

CD8 ratio) and enhancement of natural killer cell activity.^{25–27} On the other hand, a recent study did not find any direct correlation between immunological changes and vitamin B12 deficiency in patients with PA.²⁸ In our patient, cyanocobalamin was a successful treatment, and thus, we may postulate that its potential immunomodulatory properties may have been a possible mechanism for the treatment of EN.

Further studies are needed to evaluate the possible correlation of EN and AG as well as the immunoregulatory mechanism of cyanocobalamin and its association with EN.

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REFERENCES

- Requena L, Requena C. Erythema nodosum. *Dermatol Online J* 2002;8:4.
- Chowanec M, Starba A, Wiland P. Erythema nodosum – review of the literature. *Reumatologia* 2016;54:79–82.
- Blake T, Manahan M, Rodins K. Erythema nodosum – a review of an uncommon panniculitis. *Dermatol Online J* 2014;20:22376.
- García-Porrúa C, González-Gay MA, Vázquez-Caruncho M, *et al*. Erythema nodosum: etiologic and predictive factors in a defined population. *Arthritis Rheum* 2000;43:584–92.
- Tavares J, Eugénio G, Calretas S, *et al*. A link between asthenia, pallor, and jaundice. *BMJ* 2016;353:i2937.
- Langan RC, Zawistowski KJ. Update on vitamin B12 deficiency. *Am Fam Physician* 2011;83:1425–30.
- Vidal-Alaball J, Butler CC, Cannings-John R, *et al*. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. *Cochrane Database Syst Rev* 2005;3:CD004655.
- Green R, Allen LH, Björke-Monsen A-L, *et al*. Vitamin B12 deficiency. *Nat Rev Dis Primers* 2017;3:17040.
- Volkov I, Rudyoy I, Press Y. Successful treatment of chronic erythema nodosum with vitamin B12. *J Am Board Fam Pract* 2005;18:567–9.
- Milman PJ, Goldenberg SP, Scheinfeld N, *et al*. Erythema nodosum and pernicious anemia. *Dermatol Online J* 2013;19:18988.
- Annibale B, Lahner E, Fave GD. Diagnosis and management of pernicious anemia. *Curr Gastroenterol Rep* 2011;13:518–24.
- Hershko C, Camaschella C. How I treat unexplained refractory iron deficiency anemia. *Blood* 2014;123:326–33.
- Stabler SP. Clinical practice. Vitamin B12 deficiency. *N Engl J Med* 2013;368:149–60.
- Carmel R, Agrawal YP. Failures of cobalamin assays in pernicious anemia. *N Engl J Med* 2012;367:385–6.
- Yang DT, Cook RJ. Spurious elevations of vitamin B12 with pernicious anemia. *N Engl J Med* 2012;366:1742–3.

Learning points

- Pernicious anaemia may be associated with iron absorption deficit.
- Physicians should be aware of the possibility that erythema nodosum might develop in association with atrophic gastritis.
- Vitamin B12 may be considered as a possible treatment for erythema nodosum, in selected cases.

- 16 Aparicio-Ugarriza R, Palacios G, Alder M, *et al.* A review of the cut-off points for the diagnosis of vitamin B12 deficiency in the general population. *Clin Chem Lab Med* 2015;53:1149–59.
- 17 Dali-Youcef N, André E. An update on cobalamin deficiency in adults. *QJM* 2009;102:17–28.
- 18 Carmel R. How I treat cobalamin (vitamin B12) deficiency. *Blood* 2008;112:2214–21.
- 19 Wolters M, Ströhle A, Hahn A. Cobalamin: a critical vitamin in the elderly. *Prev Med* 2004;39:1256–66.
- 20 Urita Y, Watanabe T, Maeda T, *et al.* Extensive atrophic gastritis increases intraduodenal hydrogen gas. *Gastroenterol Res Pract* 2008;2008:1–4.
- 21 Dukowicz AC, Lacy BE, Levine GM. Small intestinal bacterial overgrowth: a comprehensive review. *Gastroenterol Hepatol* 2007;3:112–22.
- 22 Bures J, Cyraný J, Kohoutová D, *et al.* Small intestinal bacterial overgrowth syndrome. *World J Gastroenterol* 2010;16:2978–90.
- 23 Schwartz RA, Nervi SJ. Erythema nodosum: a sign of systemic disease. *Am Fam Physician* 2007;75:695–700.
- 24 Kunz M, Beutel S, Bröcker E. Leucocyte activation in erythema nodosum. *Clin Exp Dermatol* 1999;24:396–401.
- 25 Erkurt MA, Aydogdu I, Dikilitaş M, *et al.* Effects of cyanocobalamin on immunity in patients with pernicious anemia. *Med Princ Pract* 2008;17:131–5.
- 26 Kubota K, Kurabayashi H, Kawada E, *et al.* Restoration of abnormally high CD4/CD8 ratio and low natural killer cell activity by vitamin B12 therapy in a patient with post-gastrectomy megaloblastic anemia. *Intern Med* 1992;31:125–6.
- 27 Tamura J, Kubota K, Murakami H, *et al.* Immunomodulation by vitamin B12: augmentation of CD8+ T lymphocytes and natural killer (NK) cell activity in vitamin B12-deficient patients by methyl-B12 treatment. *Clin Exp Immunol* 1999;116:28–32.
- 28 Watanabe S, Ide N, Ogawara H, *et al.* High percentage of regulatory T cells before and after vitamin B12 treatment in patients with pernicious anemia. *Acta Haematol* 2015;133:83–8.

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