Hypomagnesemia, hypogammaglobulinemia, and chronic normocytic normochromic anemia: random association? An unresolved case report of an elderly patient with remitting seronegative symmetrical synovitis with pitting edema syndrome

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Abstract

This is the clinical case of an elderly man suffering from stabilized polypathology, affected by remitting seronegative symmetrical synovitis with pitting edema syndrome following anti-COVID vaccines, with evidence of persistent hypomagnesemia, coexisting chronic hypogammaglobulinemia and normochromic normocytic anemia. Although we investigated potential links between these conditions, the case remains partially unresolved.

Introduction

Why do we describe this case?

In the elderly, multiple pathologies and multi-drug therapies often coexist. While some diseases may be related to each other, others appear to be independent.

The incidental finding of hypomagnesemia during clinical investigations for a remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome prompted us to further investigate a possible association with non-deficiency anemia and hypogammaglobulinemia, both conditions having persisted for a long time before.

Case Report

A 74-year-old Caucasian man came to us for an evaluation in March 2022.[1] His medical history revealed: previous smoking, light alcohol intake, anal fistula surgery, previous foot phlegmon, hypercholesterolemia, hyperuricemia, arterial hypertension, carotid, and aorto-iliac atheromatosis, livedo reticularis in lower limbs, chronic gastritis, cervical spondylarthrosis, right heel spur, snoring, mild chronic normocytic normochromic anemia, and mild leukopenia (Figure 1), with mild hypogammaglobulinemia (9.9-10.3%; nv>11.1). His current therapy includes aspirin 100 mg, esomeprazole 20 mg, atorvastatin 40 mg, candesartan 16 mg + hydrochlrothiazide 12.5 mg, and sodium alginate as needed. Ten months prior, he was diagnosed with polymyalgia rheumatica and treated with nonsteroidal anti-inflammatory drugs and dexamethasone. Symptoms began three weeks after the administration of the second dose of the Comirnaty®Pfizer/BioNTech COVID-19 vac-

cine. Tests conducted during that period showed persistent mild anemia with leukopenia (Figure 1), a variable increase in inflammatory indices, negative neoplastic markers, and positive fecal occult blood.

Esophagogastroduodenoscopy and colonoscopy revealed erosive gastritis, a hyperplastic polyp of the stomach (*Helicobacter pylori*-negative), and a tubulovillous adenoma in sigmoid diverticulosis. Abdominal ultrasound was negative (reactive inguinal lymph nodes only). In mid-December, symptoms worsened with the appearance of edema in both lower limbs, marked accentuation of the livedo reticularis, and feelings of facial, abdominal, and scrotal swelling, as well as dyspnea upon physical exertion. These symptoms were accentuated after the booster dose of Spikevax®Moderna mRNA-1273. The physical examination also revealed symmetrical pitting edema in both hands' dorsum, a deficit in shoulder movement, a hydrocele, and a hypertrophic right calf (Figure 2).[1] The laboratory tests performed are indicated in Table 1. Normal: immunoglobulin E, creatine phosphokinase, lactate dehydrogenase, thyroid-stimulating hormone, nt-pro-BNP, rheumatoid factor, antinuclear antibodies, extractable nuclear antigen, anti-citrullinated protein antibodies, calcium, phosphate, activated partial thromboplastin time, international normalized ratio, ferritin, saturation of transferrin (22.2%), serum β2-microglobulin, folic acid, vitamin B12, fecal calprotectin, red blood cell osmotic resistance (RBCOR), indirect Coombs, C3c, C4.

Cryoglobulins were absent, anti-β2 glycoprotein I antibodies and anticardiolipin antibodies negative, anti-tissue transglutaminase immunoglobulin A and EMA absent, and hepatitis B and hepatitis C negative. *V617F JAK2* mutation is negative. Hands-X-ray showed no erosions, and soft tissue edema (sausage fingers). Right shoulder ultrasound showed subacromial-subdeltoid bursitis (Figure 3).[1] Scrotal ultrasound showed bilateral hydrocele. Lower limb ultrasounds revealed subcutaneous soft tissue edema in the legs, no deep vein thrombosis, bilateral Baker's cyst, and hematoma in the right medial twin muscle (from previous exertional muscle tear).

Given the hypothesis of RS3PE syndrome, the patient was treated with orally administered methylprednisolone (8

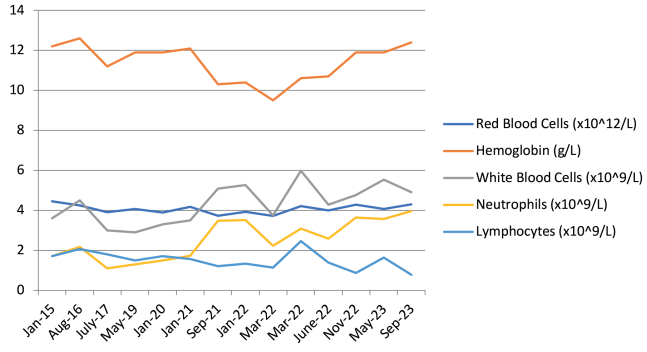

Figure 1. Summary of the evolution over time (7 years) of red blood cells, hemoglobin, white blood cells, neutrophils and lymphocytes before and after COVID-19 vaccinations (2021-2022).

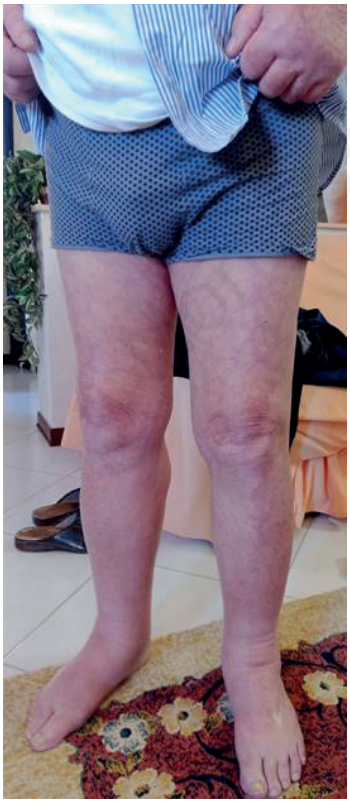

Figure 2. Patient photograph: symmetrical edema in the hands, lower limb edema, hydrocele, livedo reticularis in lower limbs. Modified from: Turrin *et al.* (2023).

Table 1. Laboratory tests performed after the medical examination.

Laboratory Tests	Results	Reference range
RBC	3.70×10^{12}/L	4.5-5.5
Hb	9.5 g/dL	13.5-16
MCV	84.7 fL	85-95
MCH	26.8 pg	27-32
MCHC	302 g/L	320-370
RDW	16.9%	11.5-14.5
Reticulocytes	$69.4\text{-}78.8\times10^{9}$/L	27-99
IRF	12.4-25.5%	2-11
Lymphocytes	1.13×10^{9}/L	1.1-4.2
Erythropoietin	22.7 U/L	2.6-18.5
γglobulin	5.9-6.1 g/L	6.4-16.2
Haptoglobin	3.97 g/L	<2
CRP	55 mg/L	<5
ESR	25 mm/h	2-37
D-dimer	2211 µg/L	<200
Magnesium	0.56 mmol/L	0.75-1.04
IgA	1.81 g/L	0.7-4.0
IgG	8.71 g/L	7-16
IgM	0.45 g/L	0.4-2.3
25(OH)D	59 nmol/L	(Insufficiency)
Homocysteine	18.9 µmol/L	<15

RBC, red blood cells; Hb, hemoglobin; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red blood cell distribution width; IRF, immature reticulocyte fraction; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Ig, immunoglobulin; 25(OH)D, 25-hydroxy vitamin D.

mg/daily), cholecalciferol 10,000 U/mL (40 drops per week), furosemide 25 mg twice daily, enoxaparine 4,000 IU aXa/0,4 mL daily (with a temporary suspension of aspirin), and orally administered magnesium (Mg) pidolate 4.50 g daily. The edema in the hands and legs quickly regressed, resulting in a 2 kg weight reduction within a week. The pain disappeared.

After three weeks, laboratory tests showed: red blood cells 4.21×10^{12}/L, hemoglobin 10.6, mean corpuscular volume 83.8, mean corpuscular hemoglobin 25.2, white blood cells 5.98×10^{9}/L, neutrophils 3.09×10^{9}/L, lymph 2.46×10^{9}/L (morphological signs of dysplasia affecting the granulocyte lineage), γglobulin 10.3, normal erythrocyte sedimentation rate and C-reactive protein, D-dimer 371, ferritin 117 µg/L (nv 25-380), Mg 0.64-0.68 (Figure 4). It should be noted that a study of lymphocyte subpopulations performed two years earlier demonstrated only a modest reduction in CD19+. Hypomagnesaemia has been related to prolonged therapy with the esomeprazole,[2,3] increased D-dimer associated with right calf hematoma. In May, 20 cc of citrine liquid was extracted with knee arthrocentesis, and the patient commenced hydroxychloroquine therapy. The laboratory tests performed in November 2022 are indicated in Table 2. Tests (24-hour diuresis: 2225 mL, body mass index 33,2) were performed after 10 days of suspension of oral Mg. Normal: serum calcium, phosphate, Na+, Cl+, K+, alkaline phosphatase, and bone-specific isoenzyme, parathyroid hormone, 24-hour urinary Na+ and K+, creatinine, cystatin C.

The flow cytometry-based assessment of lymphocyte subpopulations, despite the presence of mild lymphocytopenia (0.78-0.85×10⁹/L), revealed a preserved CD4/CD8 ratio and a significant reduction in B lymphocytes (CD19: 0.022×10^{3}/µL), comprising 68% naive B cells and 31% memory B cells. The lower-than-normal hemoglobin A2 value (1.6%), alongside normal RBCOR, could indicate δ thalassemia trait anemia (which is not pathological and not detectable by our kits) or negative results in α thalassemia trait DNA analysis for defects (molecular typing of the 22 α-globin gene). Cortisone therapy did not lead to significant increases in blood count parameters.

Following the discontinuation of prior diuretic therapy (current regimen: lercanidipine, aspirin, and esomeprazole), magnesemia monitoring during replacement therapy (oxide, 375 mg once a day) revealed levels of 0.70-0.73 mmol/L (nv: 0.75-1.04). A 24-hour urinary Mg collection yielded 1.35 mmol (nv: 3-5 mmol/24h), fractional excretion of Mg (FEMg) 1.39%, 24-hour urinary calcium 1.50 mmol (nv: 2.5-7.5), and 24-hour phosphate 12.48 mmol (nv: 12.9-42), with fractional excretion of phosphate

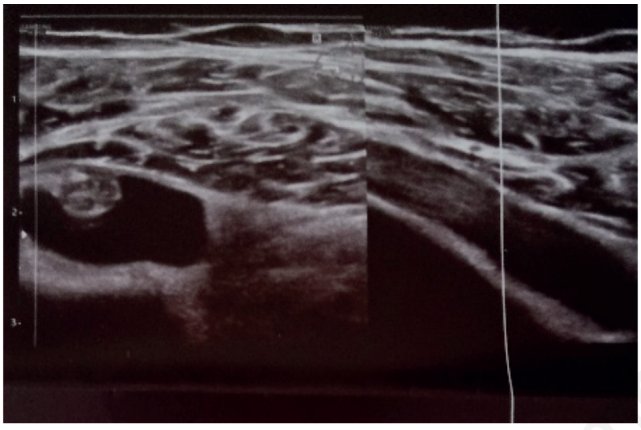

Figure 3. Image of the ultrasonographic exam of right shoulder: subacromial-subdeltoid bursitis. Modified from: Turrin *et al.* (2023).

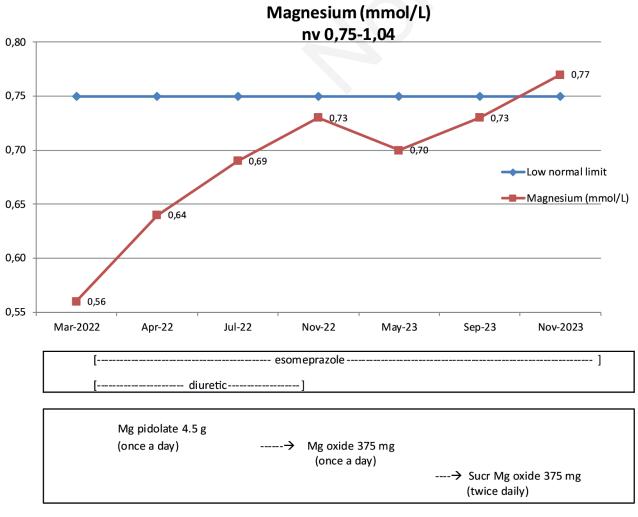

Figure 4. Summary of the evolution over time of hypomagnesemia, corrected by three different magnesium formulations. Mg, magnesium; sucr, sucrosomal.

Table 2. Laboratory tests performed in November 2022.

Parameter	Value	Reference range
RBC	4.29×10^{12}/L	4.5-5.5
Hb	11.9	13.5-16.0
MCV	90	85-95
MCH	27.7	27-32
RDW	17.8%	11.5-14.5
WBC	4.76×10^{9}/L	4.0-10.0
Lymphocytes	0.87×10^{9}/L	1.10-4.20
HbA	98.2%	96-100
HbA2	1.6%	2-3.2
HbF	0.2%	<1.5
Mg	0.73 mmol/L	0.75-1.04
24-hour urinary Mg	1.1 mmol	3-5 mmol/24 h
24-hour urinary calcium	1.1 mmol	2.5-7.5
24-hour urinary phosphate	10.2 mmol	12.9-42
Urine pH	6.5	5.0-7.0
Fractional magnesium excretion	1.45%	2-4
Fractional excretion of phosphate	8.45%	10-20
γglobulin	7.10 g/L	6.4-16.2
Total IgG	7.89 g/L	7-16
IgG-1	6.09 g/L	4.05-10.11
IgG-2	1.07 g/L	1.69-7.86
IgG-3	0.07 g/L	0.11-0.85
IgG-4	0.657 g/L	0.03-2.01

RBC, red blood cells; Hb, hemoglobin; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; RDW, red cell distribution width; HbA, hemoglobin A; HbA2, hemoglobin A2; HbF, hemoglobin F; Mg, magnesium; IgG, immunoglobulin G.

at 9.39%. Subsequently, the patient received treatment with an oral formulation of sucrosomal Mg oxide (375 mg of Mg element: 1 sachet twice daily) for 10 days, resulting in controlled magnesemia levels of 0.77 mmol/L (Figure 4).

Discussion

Our clinical case raises several unresolved questions.

The persistent mild normocytic normochromic anemia, which is unrelated to inflammatory syndromes, remains without a definitive diagnosis despite comprehensive investigations into blood counts and hemoglobin status. Persistent hypomagnesemia, attributed to prolonged proton pump inhibitor intake and possibly exacerbated by diuretic use, has not responded to Mg supplementation. The absence of current symptoms, particularly clinical signs of urolithiasis,[4] suggests the hypothesis of chronic exposure and adaptation to hypomagnesemia. Unfortunately, previous magnesemia data were unavailable, and discontinuing esomeprazole intake was not feasible due to worsened gastric disorder symptoms. The impact of replacing esomeprazole with famotidine on maintaining acceptable Mg levels remains to be established. The use of sucrosomal Mg oxide, a formulation with greater bioavailability compared to other preparations,[5] at high dosages, normalized magnesemia values. 24-hour urine collection aids in distinguishing kidney involvement from impaired gastrointestinal absorption.

The FEMg is consistent with reduced dietary Mg intake, gastrointestinal losses, and intracellular redistribution; however, the first two causes have been ruled out. Hypomagnesuria associated with hypocalciuria and hypophosphaturia raises the possibility of isolated-dominant hypomagnesemia, warranting genetic investigation.[6] Notably, having one daughter with normal magnesemia complicates the diagnostic picture. Persistent hypogammaglobulinemia, categorized as "isolated IgG subclass deficiency: IgGSD",[7] exhibits variable trends over time. The disparity between hypogammaglobulinemia values, modest immunoglobulin G4 subclass deficit, and significant alterations in lymphocyte subpopulations necessitate further exploration. The correlation with adverse reactions to anti-COVID vaccines, particularly considering the marked reduction in B lymphocytes, remains undetermined.

Conclusions

The relationships between chronic normocytic normochromic anemia, variable hypogammaglobulinemia, and hypomagnesemia in the patient remain unclear. However, potential correlations between Mg levels and the immune system should be considered. Recent research underscores the importance of Mg for effective T lymphocyte function in immunotherapy, emphasizing its role in cancer progression, infectious diseases, and inflammation.[8-10] Further investigation and correlation analysis are essential to unraveling the complexities of these interrelated health issues in the presented case.

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