

Case Report

Polymyalgia Rheumatica Evolved into RS3PE Syndrome. What is the Culprit: Idiopathic or Secondary, Following mRNA-Based COVID-19 Vaccines? A Case Report and Brief Review of the Literature

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Abstract

We describe the clinical case of a 74-year-old male patient who received the second Comirnaty/Pfizer anti-COVID-19 vaccine dose. After 3 weeks he showed the clinical signs of polymyalgia rheumatica. The history included mild chronic normocytic normochromic anemia and hypogammaglobulinemia, osteoarthritis disease, livedo reticularis, hypercholesterolemia, and arterial hypertension. Despite prolonged treatment with NSAIDs and dexamethasone, the disease evolved into remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome. Neoplastic diseases and associated collagen diseases were excluded. The clinical picture recurred, soon after, the booster dose of the Spikevax/Moderna vaccine. The inflammatory indices were high, the radiographs of the hands were free of erosions, the ultrasound investigations revealed bursitis of the shoulders, knee synovitis, marked subcutaneous edema of the lower limbs, hydrocele, bilateral Baker's cyst in



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the popliteal cavity, hematoma of a calf. The clinical picture, markedly improved, with oral prednisolone and was stabilized with the association of hydroxychloroquine. The finding of persistent hypomagnesemia was related to chronic intake of esomeprazole. The reports of rheumatological reactions in international databases and the rare cases of RS3PE syndrome following the COVID-19 vaccine described in the literature are considered.

Keywords

Polymyalgia rheumatica; RS3PE syndrome; COVID-19 vaccine; hypogammaglobulinemia; chronic normocytic anemia; hypomagnesemia; Baker's cyst; case study

1. Introduction

Amongst the side effects of the BNT162b2 mRNA COVID-19 vaccine, there have been noted general pathologies and conditions related to the area of inoculation, pathologies affecting the nervous system and someone, affecting the musculoskeletal system. Out of a total of 177,925 of all UK spontaneous adverse vaccine injuries reported in the "Yellow-Card" system between 09/12/20 and 23/11/2022 for COVID-19 Pfizer/BioNTech vaccine [1], there have been 58,340 reports of nonfatal Muscle & tissue disorders [2] including 110 numbers of polymyalgia rheumatic (PMR) reports and 27 cases of giant cell arteritis (GCA). So far there have been about 50 cases of PMR, new onset or relapse, including GCA and PMR-like, after the Comirnaty® vaccine, all published in full in the Literature [3-16]. Fewer cases were reported after the Moderna mRNA-1273 vaccine (Spikevax®) [5, 10, 17]. Of all the 26,246,383 reports in VigiBase (WHO's global Individual Case Safety Report database) dated up to June 30th 2021, 1,295,482 are spontaneous reports concerning COVID-19 vaccines (mRNA and viral vector-based), amongst which it was observed, 290 were cases of PMR (185 in Europe alone) [18, 19]. A recent Italian study from a single center cohort noted 10 cases of PMR out of a total of 30 AEFI (Adverse Events Following Immunization) reports, related to new onset and flare of rheumatic diseases, following the COVID vaccine out of a total of 6,882,395 administered doses [20].

2. Case Description

In April 2021, a 74-year-old Caucasian man was administered his first dose of the Comirnaty® Pfizer/BioNTech COVID-19 vaccine without any side effects. The following 16th of May, the very same individual in good health, was administered a second dose of the same vaccine. After three weeks paresthesia, on his left hand, was observed and cervical pain and pain in the right shoulder, positively initially treated with NSAIDs and betamethasone. The anamnesis reveals the following: ischemic heart disease and neoplasms in the family history, no immune-mediated inflammatory diseases, previous smoker, psoriasis-like dermatopathy at the age of forty, anal fistula already operated, previous right foot dorsal phlegmon, hypercholesterolemia, hyperuricemia, arterial hypertension, carotid and aortoiliac atheromasia, livedo reticularis in the lower limbs, foot onychomycosis, chronic gastritis, cervical spondyloarthritis, mild chronic normocytic normochromic anemia and mild leukopenia (Figure 1 and Figure 2), uncertain significance's mild hypogammaglobulinemia.

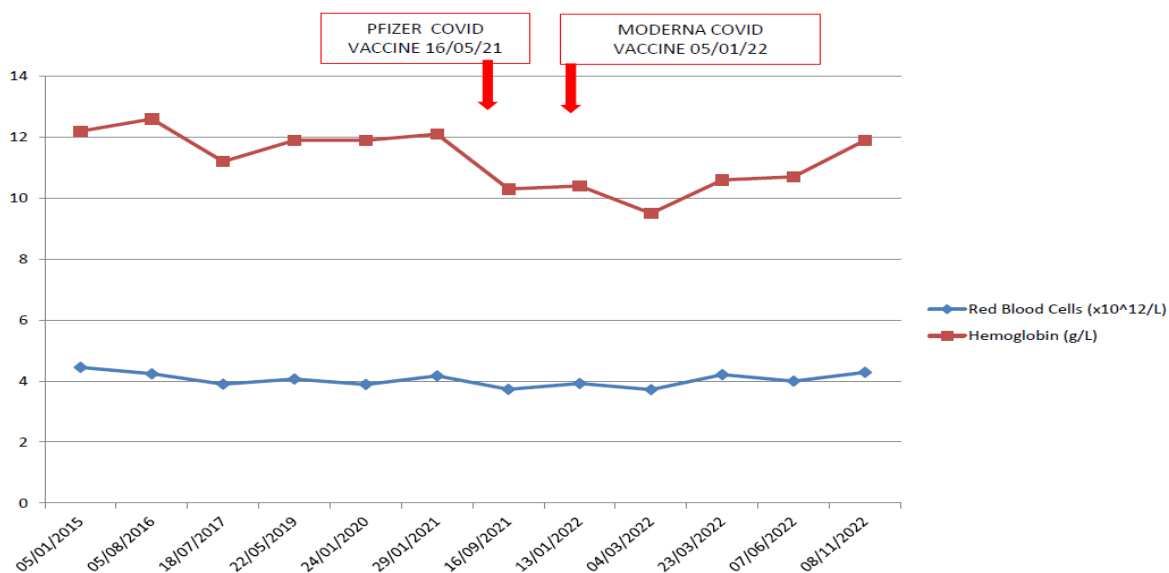


Figure 1 Summarize of the evolution of RBC and Hemoglobin before and after COVID-19 vaccinations.

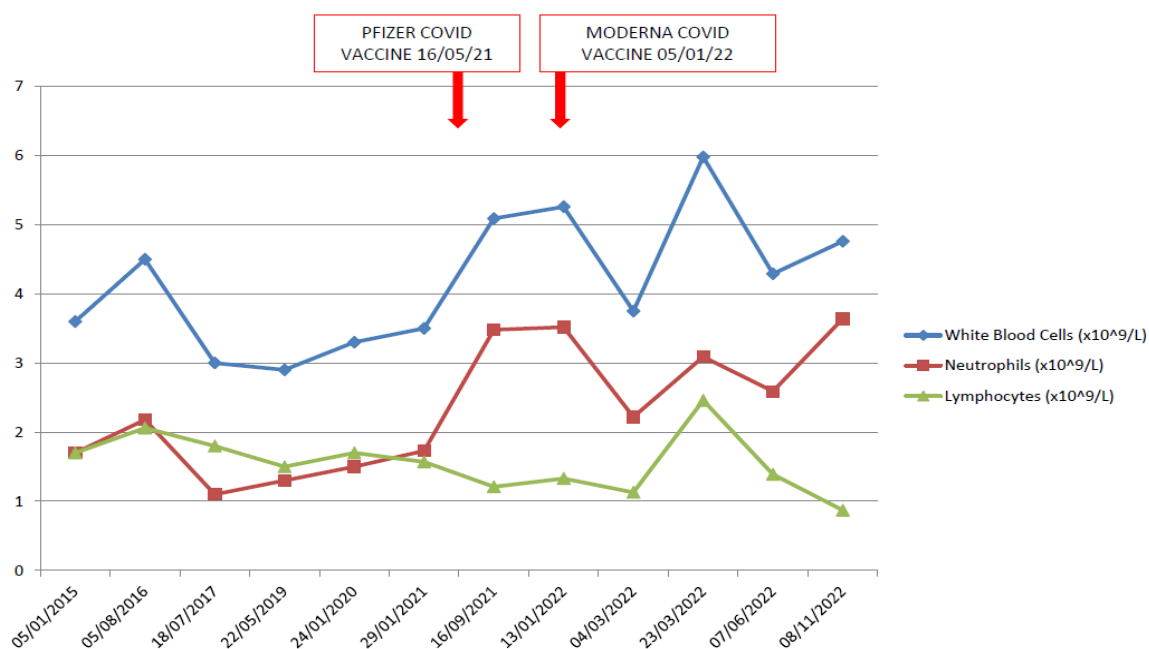
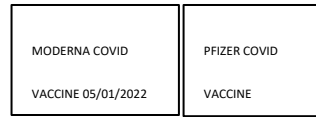


Figure 2 Summarize of the evolution of WBC before and after the COVID-19 vaccinations.

His therapy consists of esomeprazole 20 mg/daily, 100 mg of aspirin daily, atorvastatin 40 mg/daily, candesartan 16 mg + hydrochlorothiazide 12.5 mg/daily, and sodium alginate as needed. An MRI of his right shoulder, performed on July 6, showed: marked arthritic alterations at the acromion-clavicular level, the supraspinatus tendon shows marked tendon changes, especially at the insertion site, and no effusions. On the left side, similar alterations are observed though less intense. After four days, a stiff neck, pain in the shoulders and the pelvic girdles, pain in the hands

and arms associated with functional limitation, pain in the knees and, subsequently, edematous swelling of the hands as a whole, appeared. A cervical MRI showed mild arthritic changes, narrowing of the C5-C6 space, and minimal posterior protrusion of the C4-C5 and C5-C6 disc with a slight imprint on the dural sac. In the suspicion of polymyalgia-like onset, the attending physician prescribed an intramuscular injection of dexamethasone 4 mg. The injections, every 3-4 days, lasted 4 months, with periodic interruptions for a total of 30 vials, interspaced with oral therapy of paracetamol + codeine phosphate, ketoprofen, diclofenac, ibuprofen and meloxicam, but with little result. Persisting pain and tingling in the hands and wrists were observed; an X-ray of the hands showed arthritic changes at the distal and trapezius-radial interphalangeal level, bilateral rhizarthrosis with reduction of the carpometacarpal joint space of the first rays, no erosion. EMG: moderate bilateral carpal tunnel. The first laboratory tests carried out 4 months after vaccination, showed the following: CRP 8.66 mg/L (nv: 0-5), RBC $3.73 \times 10^{12}/L$, Hgb 10.3 g/dL, MCV 85.8 fl, MCH 27 pg, lymphocytes $1.21 \times 10^9/L$, gammaglobulin 5.9 g/L (nv: 6.4-16.2), uric acid 7.2 mg/dl (nv: 3.5-7); normal: renal, hepatic, thyroid function tests, RF, transferrin, ferritin, CPK, fecal calprotectin, folic acid, vitamin B12, α FP, CEA, CA 19-9, PSA (Table 1 and Table 2).

Table 1 Summarize of the laboratory tests performed before and after COVID-19 vaccinations (in bold the altered values).



Parameter	Detected level															Normal range
	05/0 1/15	05/0 8/16	18/0 7/17	22/0 5/19	24/0 1/20	29/01 /21	16/09 /21	14/1 0/21	13/0 1/22	01/0 2/22	4/03 /22	23/03 /22	07/0 6/22	07/0 7/22	08/11/20 22	
Red Blood Cells (× 10 ¹² /L)	4.45	4.24	3.90	4.07	3.89	4.17	3.73		3.92	3.70	3.72	4.21	4.00		4.29	4.5-5.5
Hemoglobin (g/L)	122	126	112	119	119	121	103		104	99.0	95.0	106	107		119	135-160
Hct (litro/litro)	0.39	0.39	0.35	0.37	0.36	0.38	0.32		0.34	0.33	0.32	0.35	0.35		0.39	0.38-0.50
MCV fL)	87.9	91.5	90.4	91.4	92.3	89.9	85.8		86.5	85.9	84.7	83.8	87.3		90	85-95
MCH (pg)	27.4	29.7	28.6	29.3	30.5	29	27.6		26.5	26.8	25.5	25.2	26.8		27.7	27-32
MCHC (g/L)	312	325	316	320	331	323	322		307		302	300	307		308	320-370
RDW (%)	16.3	16.6	16.4	16.5	16.2	16.2	16		16.6		16.9	18.2	17.2		17.8	11.5-14.5
Platelets (× 10 ⁹ /L)	203	190	173	172	178	180	314		338		399	303	278		235	150-400
White Blood Cells (× 10 ⁹ /L)	3.6	4.5	3.0	2.9	3.3	3.5	5.09		5.26		3.75	5,8	4.29		4.76	4-10
Neutrophils (× 10 ⁹ /L)	1.7	2.18	1.1	1.3	1.5	1.73	3.48		3.52		2.22	3.09	2.59		3.64	1.9-8
Lymphocytes (× 10 ⁹ /L)	1.7	2.06	1.8	1.5	1.7	1.57	1.21		1.33		1.13	2.46	1.39		0.87	0.90-4.0
Reticulocytes		87.3	68			90.5	69.4	78.8								27.1-99.0

($\times 10^9/L$)										
Reticulocytes (IRF, %)	21.6	21.5	12.4	18.9	25.5				2.0-11.0	
ESR (mm/h)				20		5			2-37	
Total iron (umol/L)		30.1		16					10.7-28.6	
Ferritin (ug/L)		125.6	120.8			163.6	117.2	86.8	25-380	
Folic acid (ug/L)				10.3	8.8				2.0-16.0	
Vitamin B12 (ng/L)				224	208				160-850	
D-dimer (ug/L)						2211	562	371	0-200	
Inorganic phosphorus (mmol/L)						1.15			0.81-1.45	
Magnesium (mmol/L)						0.56	0.64	0.69	0.73	0.75-1.04
Total calcium (mmol/L)						2.30		2.49	2.20-2.65	
LDH (U/L)					173				<248	
C-reactive protein (CRP) (mg/L)				8.66	24.3	54.9	1.84	18.2	2.53	<5

After the positive occult blood test in October, an EGDS and colonoscopy were performed with the following result: erosive gastritis, acid reflux, hyperplastic polyp of the stomach (*Helicobacter pylori*-negative) and a tubulovillous adenoma (low-grade dysplasia) in sigma mild diverticulosis. In mid-December, the symptoms worsened with the appearance of peripheral edema in the lower limbs, feeling of facial, abdominal and scrotal swelling, asthenia, dyspnea from physical exertion, erectile dysfunction and marked accentuation of the livedo reticularis in both lower limbs. Ultrasonography of the lower extremities revealed subcutaneous soft tissue edema in the legs with fluid dissociation of the fat lobes. Since then he has started therapy with furosemide (25 mg/daily) combined with multivitamins and saline supplements (the latter two assumed on their initiative). The following drugs were also discontinued as a precaution: candesartan + hydrochlorothiazide (normal blood pressure), atorvastatin (pain), esomeprazole (gynecomastia), aspirin and allopurinol (nausea). Intermittent dexamethasone therapy was suspended at the end of December given the booster dose of the anti-COVID vaccine. On January 5, Spikevax® Moderna mRNA-1273 (half dose: 0.5 mL) was administered. After three days, the pain in the upper limbs in the hands and lower limbs, and decreased appetite and dyspnoea worsened. Laboratory tests performed after 8 days showed: CPR 24.3 (nv: 0-5 mg/L), ESR 20, Hgb 10.4 g/dL, RBC $3.92 \times 10^{12}/L$, (Table 1 and Table 2). The patient comes to us for an evaluation in March 2022. The physical examination revealed: a BMI of $28.03 \text{ kg}/\text{m}^2$, symmetrical pitting edema in the dorsum of both hands with wrist edema (Figure 3 a), a deficit in the shoulder movement, and lower limb edema specifically the feet (Figure 3 a- b-c), small palpable lymph nodes in the bilateral inguinal area, bilateral hydrocele (Figure 3 a), a hypertrophic right calf, a livedo reticularis columnar in the lower limbs (Figure 3 a-b), onychomycosis on toes. Current therapy: esomeprazole, aspirin, ketoprofen or ibuprofen, furosemide, multivitamins and mineral salts.

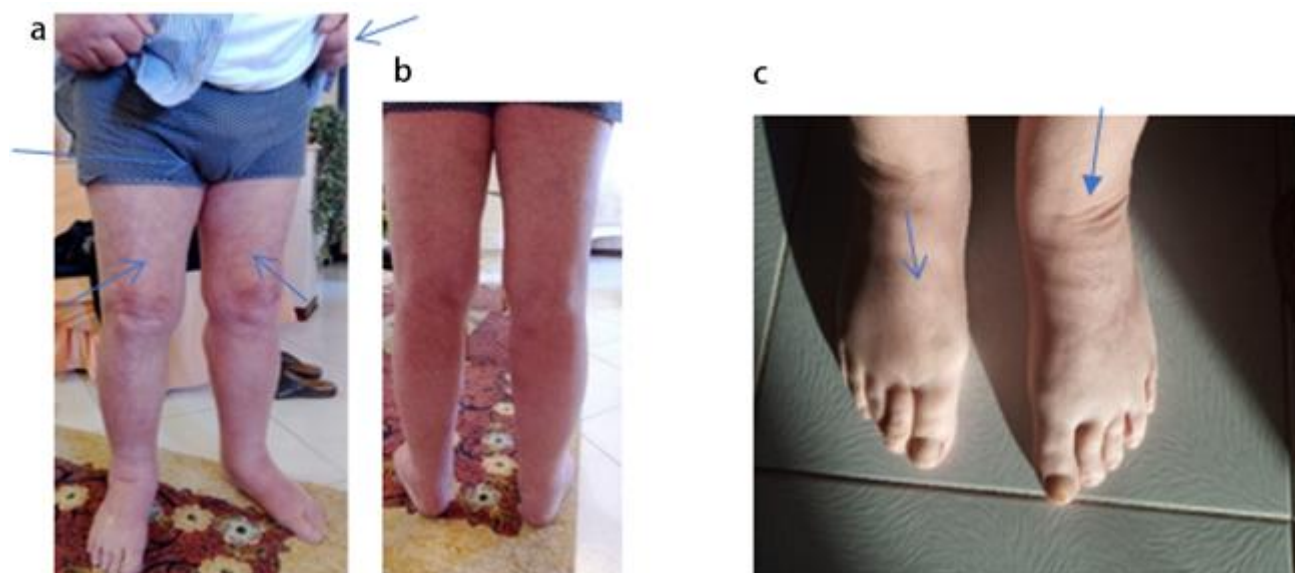


Figure 3 (a-b-c): symmetrical edema in the hands, lower limb edema, hydrocele, livedo reticularis in lower limbs (arrows).

Laboratory tests performed two months after the third dose of the Moderna vaccine (and without cortisone therapy), demonstrate the following: RBC $3.70 \times 10^{12}/L$, Hb 9.5 g/dL, MCV 84.7 fL, MCH 26.8 pg, lymphocytes $1.13 \times 10^9/L$, gamma globulin 6.1 g/L, CRP 24.3 -> 55, ESR 25 mm/h;

D-dimer 2211 µg/L (nv: <200), fibrinogen 4.90 g/L (nv: 2-4), magnesium 0.56 mmol/l (nv: 0.75-1.04), IgA 1.81 g/L (nv: 0.7-4.0), IgG 8.71 g/L (nv:7-16), IgM 0.45 g/L (nv: 0.4-2.3), IgE 48 kUa/L (nv: <150), 25-OH vitamin D 59 nmol/L (insufficiency 50-74 nmol/L). Fecal occult blood is absent. Normal: LDH, nt-pro-BNP, ANA, ENA, ACPA, calcium, phosphate, aPTT, INR, C3c, C4; cryoglobulins absent, anti-β2 GPI (IgG-IgM) and ACL (IgG-IgM) negative, anti-tTG IgA and EMA absent, serological screening for HBV and HCV negative (Table 2).

Table 2 Summarize of the laboratory tests performed before and after COVID-19 vaccinations (in bold the altered values).

MODERNA COVID VACCINE 05/01/2022	PFIZER COVID VACCINE 16/05/2021
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Parameter	Detected level															Normal range
	05/01/15	05/08/16	18/07/17	22/05/19	24/01/20	29/01/21	16/09/21	14/10/21	13/01/22	8/02/22	14/03/22	23/03/22	07/06/22	08/11/22		
Thyrotropin (mU/L)						2.93	1.01								0.35-4.5	
Total protein (g/L)						71.5	70.7					74.5	68		66-83	
Albumin (g/L)						42.2	39.3					39.7	42.23		3.2-52.1	
Alpha-1-globulins (g/L)						1.4	1.8					1.9	3.6		0.6-2.4	
Alpha-2-globulins (g/L)						10.1	11.7					9.8	6.05		5.7-11.5	
Beta-1-globulins (g/L)						7.9	7.5					8.3	4.83		3.6-7.8	
Beta-2-globulins (g/L)						3.5	4.6					4.5	3.47		1.6-4.6	
Gamma-globulins (g/L)						6.5	5.9				6.1	10.3	7.82		6.4-16.2	
Gamma-globulins (%)	9.9	10.3	10.1	9.8											>11.1	
Total bilirubin (umol/L)										11.4					1.7-17	
Sodium												143	137		136-145	

(mmol/L)						
Potassium	4.4	4.0		3.5	4.6	3.5-5.1
(mmol/L)						
Chlorine	102			101	99	98-107
(mmol/L)						
Total creatine kinase (U/L)			28			<171
Creatinine (umol/L)		70			68.26	64-104
Uric acid (umol/L)	438	429	338		409	208-428
Total cholesterol (mmol/L)	5.30					<4.92
Triglycerides (mmol/L)	1.44					<1.70
Prostate Specific Antigen (PSA) (ug/L)		1.33			0.58	<4
Prostate Specific Antigen Free/Total ratio			13		24	>20
Alkaline phosphatase (U/L)				158	54	30-120

Bone alkaline phosphatase isoenzyme (µg/L)			8.94		3-20.2
Alanine amino transferase (U/L)			12	6	<45
Rheumatoid factor (KU/L)		5.4			<14
Complement C3c (g/L)		1.76	1.30		0.9-1.8
Complement C4 (g/L)			0.40		0.10-0.40
Immunoglobulins IgA (g/L)	1.74		1.81	1.79	0.7-4.0
Immunoglobulins IgG (g/L)	6.58		8.71	7.97	7.0-16.0
Immunoglobulins IgM (g/L)	0.43		0.45	0.45	0.40-2.30
Fibrinogen (g/L)			4.9		2-4
Prothrombin time (INR)			1.2		0.9-1.97
Partial thromboplastin time (sec)			27.6		26-36
Fecal occult blood (three		Positive		Negative	

samples)				
CEA (ug/L)	0.9			0-4
CA 19.9 (KU/L)	2.7			<35.4
αFP (μg/L)	3.3			0-12
Fecal				
calprotectin	12			<100
(ug/gr)				
ANA (titre)		<1:8		<1:80
		0		
Anti-cyclic				
citrullinated				
peptide		0		<7
(ACPA) (U/ml)				
Anti-				
cardiolipin IgG			Abse	Absent
e IgM			nt	
Anti-β2			Abse	Absent
Glicoprotein I			nt	
Anti-			Abse	Absent
transglutamin			nt	
ase IgA				
Anti-			Abse	Absent
endomysial			nt	
IgA				
Cryoglobulins			Abse	Absent
			nt	
25-OH-D			59.5	116.8 75-250
Vitamin				

(nmol/L)			
IgE			
immunoglobul	48.1		<150
ins			
PTH (ng/L)		27.10	8.7-79.6
IgG			
subclasses:		6.09	4.05-7.86
IgG 1 (g/L)			
IgG 2 (g/L)		1.07	1.69-7.86
IgG 3 (g/L)		0.07	0.11-0.85
IgG 4 (g/L)		0.657	0.03-2.01

A complete abdominal ultrasound was negative except for bilateral reactive inguinal lymph nodes. Hands-X-ray (a technique for soft parts): unchanged compared to the previous ones, no erosions, soft tissue edema ("sausage" fingers) (Figure 4 and Figure 5).



Figure 4 X-ray (technique for soft part) left hand.



Figure 5 X-ray (technique for soft part) right hand.

Right shoulder ultrasound: liquid distension of the subacromiondeltoid bursa (Figure 6), liquid distension of the tendon sheath of the long head of the humeral biceps with a finely inhomogeneous appearance (degenerative tendinopathy + synovitis), the tendon of the supraspinatus muscle appears thickened and inhomogeneous.



Figure 6 Right shoulder US (trasverse subacromial anterior view): bursitis.

Scrotal ultrasound: bilateral hydrocele, varicocele on the left. Breast ultrasound: true bilateral true gynecomastia. EKG: sinus rhythm, LAH. Echocardiogram: EF >60%, left atrial enlargement (49 ml/m²: nv: 16-28), aortosclerosis. Chest-X-ray: alone aortosclerosis. Ultrasonography of venous lower limbs: no deep vein thrombosis, edema of the subcutaneous soft tissues of the legs with fluid dissociation of the adipose lobules. Lower limbs musculotendinous US: voluminous Baker's cyst to the left popliteal fossa, extended by 10 cm (Figure 7), analogous to 2.7 cm on the right (Figure 8), serum haematic effusion in the right medial twin muscle (from previous exertional muscle tear) (Figure 9).



Figure 7 Lower limbs musculotendinous US left popliteal fossa: voluminous liquid distension of the mucosal bursa of the gastrocnemius-semimebranosus muscle, multichambered, extended longitudinally for 10 cm.

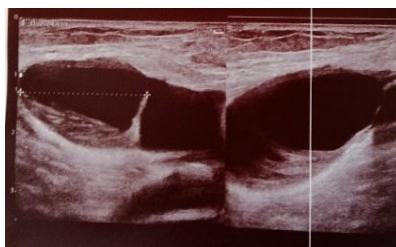


Figure 8 Lower limbs musculotendinous US right popliteal fossa: liquid distension of the mucosal bursa of the gastrocnemius-semimembranous muscle, multichambered, extended longitudinally for 2.7 cm.



Figure 9 Left calf US: below Baker's cyst in the context of the medial twin muscle there is an in homogeneously organized serum-haematic effusion (5.3 × 1.2 cm in size).

The patient was then treated with methylprednisolone taken orally (8 mg/daily), cholecalciferol 10,000 U/ml: 40 drops/week, furosemide 25 mg bid, enoxaparin 4,000 U.I. aXa/0.4 ml/daily (temporary suspension of aspirin), magnesium picolinate 4.50 g/daily. The edema in the hands and legs quickly regressed, the weight was reduced by 2 kg weekly, pain and erectile deficit disappeared, and cenesthesia improved. After three weeks of therapy, the laboratory tests showed: RBC $4.21 \times 10^{12}/L$, Hgb 10.6, MCV 83.8, MCH 25.2, lymphocytes $2.46 \times 10^9/L$, gamma globulin 10.3, ESR 5, RCP 1.84, Mg 0.64 ($->0.68$), D-dimer 371, ferritin 117, stool test for occult blood negative (Table 1 and Table 2). Increased D-dimer was associated with right calf hematoma; hypomagnesemia has been related to prolonged therapy with the proton pump inhibitor esomeprazole [21].

After 2 months, the well-tolerated dosage of the steroid was halved. The patient complained of pain in the left knee: in May an arthrocentesis was performed with 20 cc of citrine liquid extraction (triamcinolone acetonide 20 mg infiltration); the patient was started on hydroxychloroquine therapy 200 mg: 2 c per day for 5 days/week. After one month of HCQ therapy, an eye check revealed no signs of maculopathy. The checking of the lower limbs showed the absence of the hematoma, while the size of the Baker's cysts was unchanged. After two months, the left Baker's cyst ruptured spontaneously. The most recent laboratory tests, while in therapy with methylprednisolone 4 mg every other day + HCQ, showed: RBC $4.29 \times 10^{12}/L$, Hgb 11.9 g/L, MCV 90 fL, MCHC 308 g/L, WBC $4.76 \times 10^9/L$, lymphocytes $0.87 \times 10^9/L$ (nv: 0.9-4.0), serum magnesium 0.73 mmol/L, serum phosphate 1.15 mmol/L, intact PTH: 27.10 ng/L (nv: 8.7-79.4), 25-OH-D vitamin: 116.8 nmol/l (enough: 75-250), ALP 54 U/L (30-120). Normal: creatinine, serum Na⁺, Cl⁻, K⁺, CRP 2.53 mg/dL, IgA: 1.79 g/l, IgG: 7.97 g/L, IgM: 0.45 g/L (nv: 0.40-2.30). IgG totali: 7.89 g/L (nv: 7-16), IgG-1: 6.09 g/L (nv: 4.05-10.11), IgG-2: 1.07 g/L (nv: 1.69-7.86), IgG-3: 0.07 g/L (nv: 0.11-0.85), IgG-4: 0.657 g/L (nv: 0.03-2.01) (Table 2).

3. Discussion

In the present study, we report a rheumatic polymyalgia case, diagnosed using the 2012 EULAR/ACR classification criteria [22], arising 3 weeks after a second dose of the mRNA-based Pfizer vaccine and evolving into remitting seronegative symmetrical synovitis with pitting edema (RS3PE) in an elderly patient. The disease flare occurred after a third dose of the mRNA-based Moderna vaccine. The clinical picture markedly improved with prednisolone and was stabilized with the association of hydroxychloroquine. Hydroxychloroquine has been used as a steroid-sparing drug to avoid the complications of chronic low-dose steroid therapy [23], replacing methotrexate for the

presence of hypogammaglobulinemia and chronic anemia. RS3PE is a rare benign rheumatic syndrome affecting elderly males. It is characterized by an acute onset of symmetrical marked pitting edema and small joint synovitis involving mainly the hands and, less often, the feet. High inflammatory markers, a negative rheumatoid factor, an absence of radiographic joint erosions and a prompt response to low-dose steroids, are hallmarks of the disease [24]. The pathogenesis of RS3PE remains largely unknown. Although most cases are idiopathic, RS3PE has been associated with other rheumatic conditions (PMR, Sjögren's syndrome, spondyloarthropathies, RA, SLE), malignancies, parvovirus infection, intravesical BCG instillation and more recently with immunotherapies [25]. We did not find any neoplastic pathologies in the follow-up of almost two years. In the absence of alternative causes, the association with the vaccine remains plausible even though only five cases (Table 3) are described in the literature. Our clinical case has some similarities concerning the five reports in which, moreover, a prolonged period between the injection's vaccine and the symptoms' onset appears to be only one. A previous case series study described an 83-year-old female with a history of polymyalgia rheumatica who developed RS3PE, seven days after the first dose of the BNT162b2 mRNA vaccine [3]. The patient had a prompt response to treatment and a further resolution of her symptoms. Another case described in the literature [26] refers to an 80-year-old man who developed a progressive RS3PE two days after the Pfizer vaccine's second dose. A third report concerns a 65-year-old man with an acute onset of RS3PE two weeks after the second dose of the mRNA-1273 Moderna vaccine with possible activation of parvovirus B19 [27]. The fourth case refers to an 81-year-old man three days after receiving his third dose of the Pfizer vaccine [28]. The last case concerns an 83-year-old woman with an exacerbation of palmar-plantar psoriasis associated with hands edema and wrist tenosynovitis, 48 hrs after the second administration of the Pfizer vaccine [29] (Table 3).

Table 3 Describes the 5 cases of RS3PE syndrome after the mRNA-based COVID-19 vaccine currently in the literature.

Author	Country	Year of publication	Patient age	Patient sex	Patient ethnicity	Pre-vaccine history	Vaccine name	Dose (number)	Days from vaccine to new-onset (number)	Severity	Associated pathologies	Relevant lab tests	Therapy	Reference
Watad A.	UK	2021	83	F	Caucasian	Hypothyroidism, polymyalgia rheumatica	Pfizer	1st	7	Severe		CRP 74 (nv <5 mg/L)	Prednisolone 15 mg/daily	[3]
Parperis K.	Cyprus	2021	80	M	Caucasian	Hypertension, hyperlipidaemia, atrial fibrillation, aortic valve stenosis, COPD, ischemic cardiomyopathy, sleep apnoea	Pfizer	2nd	2	Moderate		CRP 120 (nv <5 mg/L) ESR 55 (nv × 20 mm/hour)	Paracetamol, prednisolone 15 mg/daily	[26]
Arino H.	Japan	2022	65	M	Japanese	Angina pectoris, recurrent urinary tract infection	Moderna	2nd	14	Moderate	Activation of parvo-virus (IgG e IgM)	CRP 26.93 (nv 14 mg/dL)	Topical NSAIDs, prednisolone 15 mg/daily	[27]
Quattrini	Italy	2021	83	F	Caucasian	Psoriasis,	Pfizer	2nd	2	Moderate	Exacerbatio	Acute phase	Prednison	[29]

It should be noted that in studies of the development of immune-mediated inflammatory diseases (IMIDs), new onset and flare, following COVID-19 vaccination, is considered a time space within 21-30 days after each dose of vaccine administered [3, 14, 20, 30]. In the group "Muscle & tissue disorders," the RS3PE syndrome does not appear among the 58,340 spontaneous reports of the English Pfizer Yellow Card system [2]. In this report, until 23rd November 2022, the following categories of symptoms and pathologies are described with numerical values (in addition to the 110 cases of PMR) which, in decreasing order of frequency, are represented by: pain in the extremities (15,175), myalgia (12,282), arthralgia (11,059), back pain (3,018), neck pain (2,344), limb discomfort (1,727), musculoskeletal stiffness (1,581), muscle weakness (1,261), bone pain (475), arthritis (445), peri arthritis (310), rheumatoid arthritis (165), fibromyalgia (156), musculoskeletal pain (151), musculoskeletal discomfort (135), bursitis (117), osteoarthritis (70), polyarthritis (18), synovitis (16). With regards to a similar English report relating to the monovalent Moderna vaccine, up to the same date, the RS3PE syndrome did not appear: only 22 cases of polymyalgia rheumatica were indicated out of 17,072 reports relating to the "Muscle & tissue disorders" group, out of a total of 47,045 Yellow cards reports [31]. According to some researchers both PMR and RS3PE, caused by mRNA anti-COVID-19 vaccines, can fall into the autoimmune/inflammatory syndrome induced by adjuvants (ASIA) also called Shoenfeld syndrome [32-34].

4. Conclusions

In the description of this clinical case the following questions remain open:

- i) The classification of pre-existing, and persistent, mild normocytic normochromic anemia, in any case unrelated to these inflammatory syndromes: further in-depth research on blood counts and hemoglobin status has not led to a definitive diagnosis.
- ii) The finding of persistent hypomagnesemia, which cannot be corrected with supplementation and attributed to the prolonged use of PPIs: unfortunately it was not possible to trace pre-vaccinal magnaemia and it was not possible to suspend the intake of esomeprazole due to the exacerbation of gastric disorder.
- iii) It is impossible to determine when Baker's cysts appeared and their association with PMR/RS3PE syndrome.
- iv) The clinical diagnosis of PMR and RS3PE syndrome with the much plausibility of an adverse reaction to mRNA-based vaccines: if the interval between the Pfizer vaccine's injection and symptoms may seem much too long, an exacerbation of the disease must be reported immediately after the third half dose of the Moderna vaccine.

Currently in the literature there are only five reports of RS3PE syndrome and rare cases of PMR after anti-COVID vaccinations. Shoenfeld's ASIA syndrome could cover our case.

The description of this clinical case, which led to very prolonged and annoying evolution for the patient, does not constitute a serious adverse reaction to the vaccine and does not negatively affect the need for anti-COVID vaccination in times of pandemic.

Abbreviations

AEFI	Adverse Event Following Immunization
ASIA	Autoimmune/Inflammatory Syndrome in response to Adjuvants
GCA	Giant Cells Arteritis

HCQ	hydroxychloroquine
IMIDs	Immune-mediated inflammatory disease
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
PMR	Polymyalgia Rheumatica
PPIs	proton pump inhibitors
RA	Rheumatoid Arthritis
RS3PE	Remitting Seronegative Symmetrical Synovitis with Pitting Oedema
SLE	Systemic lupus erythematosus
VigiBase	WHO Adverse Drug Reaction Database

Author Contributions

Mauro Turrin produced the conceptualization of the article, the writing of the text and the collection of all the clinical data. Lucia Fornasiero performed the laboratory data processing. Antonio Navarro provided radiological iconography with related comments.

Competing Interests

The authors have declared that no competing interests exist.

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