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CASE REPORT

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Remitting seronegative symmetrical synovitis with pitting edema syndrome: case report of an atypical presentation of a rare syndrome and literature review

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Abstract

Background Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) is a rare syndrome. The following case shows an atypical course of the disease with successful treatment. In addition, the accompanied review highlights current findings in the pathogenesis and treatment. Clinicians should be aware of the differential diagnosis of RS3PE syndrome.

Case presentation A 67-year-old female patient with recurrent, asymmetric, and painful swelling of both hands with pitting edema, predominantly affecting the dorsal right hand, presented at our in-patient clinic. Over the years of her disease, first diagnosed as rheumatoid arthritis and then psoriatic arthritis, prednisolone treatment had the most favorable effects over various disease-modifying antirheumatic drugs.

Subsequent diagnostic evaluation confirmed RS3PE syndrome, a rare inflammatory disorder primarily affecting the elderly population. Manifesting as symmetrical joint inflammation of small joints with pitting edema, RS3PE syndrome typically onsets suddenly and may be accompanied by systemic symptoms like fever, fatigue, and weight loss. Although the precise etiology remains enigmatic, both the innate and the adaptive immune system seem to play a pathogenic role. Treatment is conventionally based on prednisolone, which effectively mitigates symptoms.

Ultimately, RS3PE was diagnosed in the context of psoriatic arthritis without dermatological or nail involvement. Given the unusual presentation marked by female gender, asymmetry, and prolonged and extensive disease with various prior treatments and in the context of psoriatic arthritis, a tumor necrosis factor alpha inhibitor was initiated in addition to low-dose prednisolone resulting in clinical remission for the first time.

Conclusions In conclusion, the aforementioned atypical manifestation highlights the significance of including RS3PE syndrome as a potential differential diagnosis, particularly in instances where specific diagnostic criteria for rheumatoid arthritis, polymyalgia rheumatica, or psoriatic arthritis are absent. RS3PE responds well to the administration of prednisolone. In refractory cases, a therapeutic trial with tumor necrosis factor alpha inhibitors can be conducted.

Keywords RS3PE, Psoriatic arthritis, Synovitis, Tenosynovitis

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Background

Remitting seronegative symmetrical synovitis with pitting edema (RS3PE), formerly described as a distinct and definite clinical entity with excellent prognosis [1, 2], is nowadays regarded as a syndrome [3] with qualities of an autoimmune and autoinflammatory disease [4]. First

characterized by McCarty et al. in 1985, RS3PE presents a unique set of clinical features that challenge its recognition and differentiation from other rheumatologic conditions [5].

RS3PE typically manifests in elderly individuals above 50 years of age with a peak at 70–79 years [6], marked by an abrupt onset of symmetric polyarthritis/synovitis with the distinguishing hallmark of pitting edema involving the dorsal hands and feet, imparting a characteristic swollen appearance [7]. This edema can lead to significant functional impairment, adding to the diagnostic complexity. Additionally, RS3PE can exhibit extra-articular manifestations, including systemic symptoms like fever, malaise, and weight loss [3, 8]. RS3PE often occurs in older men in the context of neoplasia. The disease is usually self-limiting after a few months of glucocorticoid treatment [9].

The diagnostic challenge of RS3PE lies in its clinical overlap with other conditions, including seronegative rheumatoid arthritis (RA), polymyalgia rheumatica (PMR), psoriatic arthritis (PsA), and paraneoplastic disorders [10]. Seronegativity for rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) helps to distinguish RS3PE in part from RA [11]. In rare cases, PMR leads to pitting edema of both hands very similar to R3SPE; however, proximal muscle weakness (shoulder/neck and pelvic girdle) and tendinitis/bursitis help to distinguish between both and are classic for PMR [12]. Psoriatic skin or nail involvement as well as typical bone changes like periostitis or the pencil-in-cup phenomena helps to differentiate between PsA and RS3PE [13]. Weight loss, fever, and nightly accentuated perspiration should lead to oncologic check-up to rule out paraneoplasia as a cause for RS3PE.

However, with the latest paradigm shift of RS3PE, being a syndrome rather than a distinct disease entity differentiating RS3PE from RA or PsA seems less important. On the contrary, in daily practice, one should be able to distinguish RS3PE syndrome when apparent, even if it manifests on top of established RA or PsA. Laboratory investigations may reveal elevated acute phase reactants such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) [14]. Imaging studies, such as ultrasound and magnetic resonance imaging (MRI), can aid in assessing joint inflammation and ruling out other pathologies [15, 16]. Compared with patients with RA, patients with RS3PE syndrome show less severe articular synovitis and no osseous erosions, as well as more and severe tenosynovitis of both extensors and flexors. Especially, tenosynovitis is a hallmark of RS3PE and often accounts for the pitting edema (extensor tenosynovitis) [5, 17]. However, flexor as well as extensor tendons can be affected [17]. Due to the (flexor) tenosynovitis, secondary carpal tunnel syndrome can be found often [18]. Therefore, imaging is most eligible to differentiate between RS3PE and other rheumatic and musculoskeletal diseases.

Glucocorticoids represent the mainstay of treatment for RS3PE, often leading to rapid improvement in symptoms. Low-dose glucocorticoid therapy has been shown to effectively suppress inflammation and alleviate edema, leading to a notable amelioration in joint symptoms [19]. In comparison to RA in elderly patients, glucocorticoid treatment in RS3PE is often required over a longer period of time [9]. Therefore, cautious monitoring for potential adverse effects associated with glucocorticoid use is advised. In the affected RS3PE population (mostly elderly patients), glucocorticoid-associated osteoporosis and infection are important side effects that need to be monitored closely [20, 21]. The role of disease-modifying antirheumatic drugs (DMARDs) remains less established, with further research needed to elucidate their potential benefits in RS3PE management [4].

RS3PE generally carries a favorable prognosis, with a majority of patients showing substantial clinical improvement upon treatment. Swift initiation of glucocorticoid therapy often leads to rapid resolution of symptoms, including joint pain, edema, and functional limitations. However, relapses can occur upon glucocorticoid tapering, necessitating a vigilant approach to follow-up care. Additionally, the potential relationship between RS3PE and malignancies warrants ongoing investigation, emphasizing the need for comprehensive patient evaluation [22, 23].

This case report is about a female patient with a persistent disease over several years, which is largely refractory to immunomodulatory therapy with DMARDs and an atypical clinical presentation of RS3PE syndrome who achieved clinical remission with tumor necrosis factor alpha therapy (TNFi) and low-dose prednisolone therapy.

The intention of publishing this case report on RS3PE syndrome arises from the fact that this case represents a rare presentation of a rare syndrome. Moreover, our case report highlights the diagnostic challenges we faced with our patient and provides valuable information on the differential diagnosis that can assist in achieving an accurate diagnosis. Lastly, we discuss the management strategies employed, including both pharmacological and non-pharmacological measures, which may serve as a guide for colleagues treating similar cases.

Case presentation

Patient presentation and clinical findings

The 67-year-old female patient presented to our rheumatologic in-patient clinic with increasing painful swelling up to edema on the back of both hands (right > left)

for 8 weeks and morning stiffness of the hand and finger joints of about 30 to 60 min daily. In addition, there were tingling paresthesias in the area of the thumb up to the middle finger of the right hand. The patient reported edema of the lower legs as well, but not of the ankles or forefeet, which is treated intermittently with loop diuretic. Occasionally, there would be fever episodes lasting several days up to 39.5 °C.

For the last 7 years, recurrent swellings occurred in the area of the dorsal hands (especially on the right side), which (so far) regressed under short-term prednisolone therapy of up to 30 mg/day with following reduction scheme. Under the suspected diagnosis of RA and/or PsA, therapy attempts with conventional synthetic (cs)-DMARDs either with methotrexate or leflunomide were made, each of which was discontinued due to insufficient efficacy or intolerance (leucopenia, nausea with vomiting, diarrhea). Furthermore, the patient was treated with various biological (b)- and target synthetic (ts)-DMARD therapies. Tocilizumab, ixekizumab, ustekinumab, and tofacitinib were all administered without sufficient efficacy and consequently terminated. Therapy with etanercept led to a significant clinical improvement in symptoms but was discontinued due to recurrent infections. Currently, a therapy with upadacitinib was performed but only administered three times a week due to side effects (sensory disturbances) with daily administration, which did not provide any relief at this dose (cf. Table 1).

Prior to the onset of symptoms, a vaccination against tick-borne encephalitis (TBE) virus was administered.

There is no known family history of any inflammatory rheumatologic diseases. Neither psoriasis nor inflammatory bowel diseases were present in the patient or in her family history. The patient did not suffer from recurring eye infections or uveitis diagnosed by an ophthalmologist.

In 2006, the patient underwent the Wertheim-Meigs surgery with curative intent for the management of serous papillary adenocarcinoma of the ovary, which was accompanied by endometrioid endometrial carcinoma and peritoneal carcinomatosis. Subsequently, the patient received six cycles of carboplatin/taxol chemotherapy. Throughout the regular postoperative monitoring, the patient has demonstrated a sustained absence of cancer recurrence up until the present time.

Thyroidectomy was performed in 1993 and 2013 for present cold nodules. A resulting hypothyroidism is substituted with L-thyroxine.

Previously, a decrease in bone density in the sense of osteopenia was known, which was treated with a substitution of 1000 IU cholecalciferol per day. The patient had chronically elevated intraocular pressure with a known history of glaucoma.

The patient does not drink alcohol regularly and has never smoked.

On physical examination, tenderness and pitting edema in both wrists (right > left) were evident (cf. Fig. 1). The metacarpophalangeal (MCP) joints of the right fingers (D2–5) were swollen with accompanying rubor and calor. Volar flexion was painfully in both hands. The Gaenslen sign was positive on the right and negative on the left. Lower extremity edema was present without concomitant tender ankle joints, intertarsal joints, tarsometatarsal joints, or metatarsophalangeal joints.

With the exception of edema, the patient presented with no other localized skin or nail changes.

The patient presented with stable vital signs and presented afebrile on admission.

Diagnostic assessment

The laboratory data on admission showed normal values for CRP and ESR.

RF as well as ACPA were repeatedly negative at first presentation and in the further course. The antinuclear antibodies (ANA) titer was never relevantly elevated. Antineutrophil cytoplasmic antibodies (ANCA) were repeatedly negative (cf. Table 2).

Table 1 Timeline of rheumatologic medical history

19 March 2014	Onset of symptoms: painful swelling of the back of the hand on the right side, recurrent fever up to 39.5 °C
14 January 2015	Rheumatologic initial referral: elevated CRP 2.7 mg/dl, MRI highly active polyarthritis of both hands, initiation methotrexate 15 mg p.o. 1 ×/week (leukopenia, nausea)
04/2017	Etanercept 50 mg s.c. 1 ×/week (recurrent infection, mostly urinary tract infections)
12/2017	Tocilizumab 162 mg s.c. 1 ×/week (no efficacy, nausea)
03/2019	Tofacitinib 5 mg 1–0-0 (no efficacy, erysipelas)
06/2019	Ixekizumab 80 mg s.c. 1 ×/4 weeks (no efficacy)
04/2021	Stelara 90 mg s.c. 1 ×/12 weeks + leflunomide 20 mg daily (no efficacy)
10/2021	Leflunomide 20 mg daily + upadacitinib 15 mg daily (side effects: sensory disturbances)
02/2022	Upadacitinib 15 mg p.o. 3 ×/Woche (no efficacy)

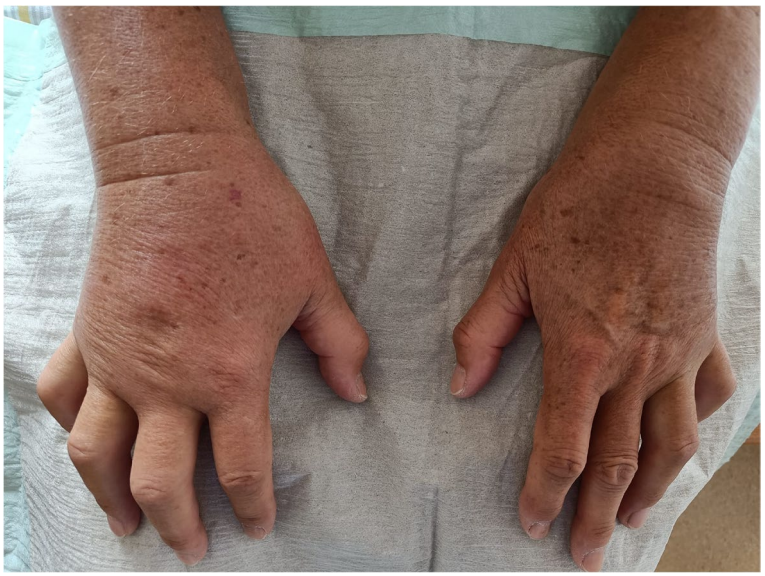

Fig. 1 Clinical presentation ad admission. The clinical picture shows a right accentuated swelling of the dorsal right hand. By pressing on the back of the right hand, a compressible edema is visible. Furthermore, the stretch inhibition of the long fingers of both hands is also visible here

Table 2 Laboratory findings ad admission

Laboratory value (reference value)	Value ad admission
Hemoglobin (ref.: 12–16 g/dl)	12.4
Mean corpuscular hemoglobin (MCH) (ref.: 28–32 pg)	30.4
Mean corpuscular volume (MCV) (ref.: 85–95 fl)	**96.3**
White blood cell count (ref.: 3.5–10 Ts/µl)	7.13
Platelets (ref.: 150–450 Ts/µl)	371
Erythrocyte sedimentation rate (ref.: < 30 mm 1st hour)	13
Creatine kinase (ref.: 26–192 U/l)	164
Lactate-dehydrogenase (LDH) (ref.: 135–214 U/l)	**246**
Creatinine (ref.: 0.5–0.9 mg/dl)	0.83
GFR (ref.: 80–140 ml/min/1.73 m^2)	**72.69**
Urea (ref.: 17–49 mg/dl)	33
Uric acid (ref.: 2.4–5.7 mg/dl)	4.6
Glutamate oxaloacetate transaminase (GOT) (ref.: 10–35 U/l)	32
Glutamate pyruvate transaminase (GPT) (ref.: 10–35 U/l)	25
Alkaline phosphotase (ref.: 35–104 U/l)	56
C-reactive protein (ref.: 0.0–0.5 mg/dl)	0.1
Thyroid-stimulating hormone (TSH) (ref.: 0.27–4.2 µU/ml)	0.55
Rheumatoid factor (ref.: 0.1–14 IU/ml)	9.2
Anti-citrullinated protein antibodies (ref.: 0–17 U/ml)	< 8
Antinuclear antibodies	Negative
ANCA	Negative
HLA B27	Negative
Hepatitis B surface antigen (HBs)	Negative
Anti-hepatitis B core antibody	Negative
Anti-hepatitis C antibody	Negative
Anti-hepatitis B-surface antibodies (ref.: < 10 mIU/ml)	2.0
TB-interferon-gamma-release test (QuantiFERON)	Negative

X-ray showed no osseous erosions. Periarticular osteoporosis was detected as an indirect sign of arthritis. Extension inhibition of the fingers of both hands was present (cf. Fig. 2).

Discrepancy to clinical examination arthrosonography and MRI showed polyarthritis of both wrist and metacarpophalangeal joints and marked tenosynovialitis of the extensor and flexor tendons of both hands (cf. Fig. 3). In the MRI studies, the right hand, which was clinically swollen with pitting edema, had significantly more tenosynovitis in comparison and presented a significant subdermal edema (cf. Fig. 4).

The anamnestic findings indicative of carpal tunnel syndrome (nocturnal paraesthesia of the first three digits of the left hand) were corroborated through ultrasonography: assessment of the cross-sectional area (CSA) of the median nerve at the level of the os pisiform unveiled a CSA of 19 mm^2 (within the normal range being up to 14 mm^2).

Differential diagnosis included R3SPE syndrome, RA, PsA, polymyalgia rheumatica, and connective tissue disease like lupus erythematosus or systemic sclerosis or gout. With massive edema of the dorsum of the right hand, negative RF, and a prompt improvement on prednisolone in the patients' medical history, we diagnosed RS3PE syndrome. Considering the multi-year course, gender, side asymmetry of the manifestation, and treatment refractory of csDMARDs (methotrexate and leflunomide) and b – as well as tsDMARDs, we assumed an atypical RS3PE syndrome that had been formerly diagnosed first as seronegative RA and later as PsA.

Therapeutic intervention

A prednisolone therapy with initially 20 mg/day as well as an intensified physical therapy (serial local cold applications, whole-body cryotherapy, and lymphatic drainage) were administered.

Due to the present comorbidities osteopenia and chronically elevated intraocular pressure, prednisolone therapy should be as low as possible. Therefore, we started a steroid-sparing medication.

In recognition of the good efficacy of the TNFi etanercept, which had to be discontinued due to side effects, we initiated adalimumab, a second TNFi.

Reinforcing our reasoning, it has been shown that atypical RS3PE syndrome can occur as a sole manifestation in the setting of PsA, and that, in addition to prednisolone therapy, TNFi therapy can lead to clinical remission [24].

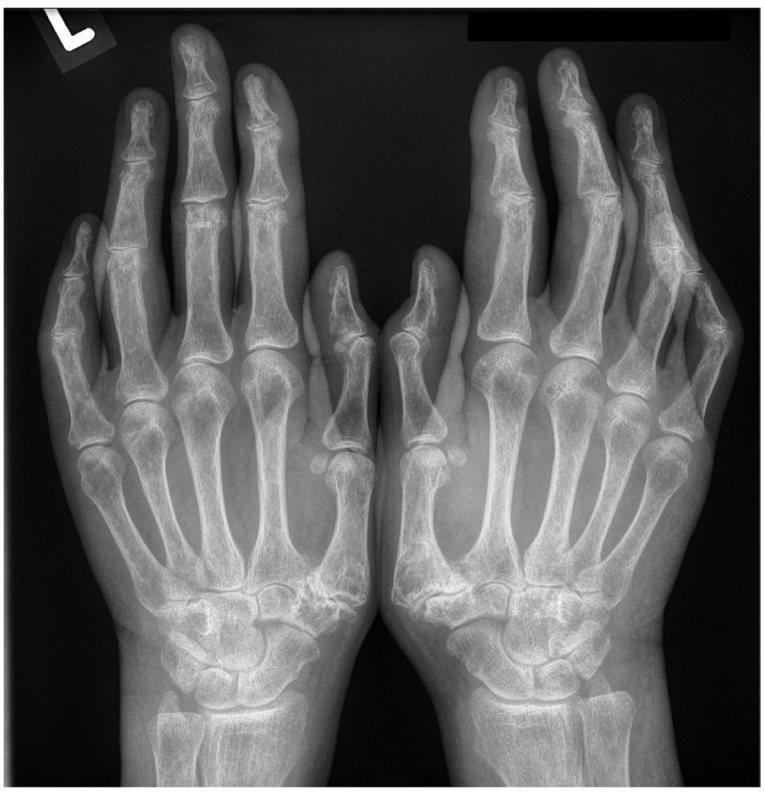

Fig. 2 X-ray hands dorso-volar. X-ray of the hand shows no osseous erosions. Periarticular osteoporosis as an indirect sign of arthritis is evident. On the right side, an extension inhibition of the long fingers is visible

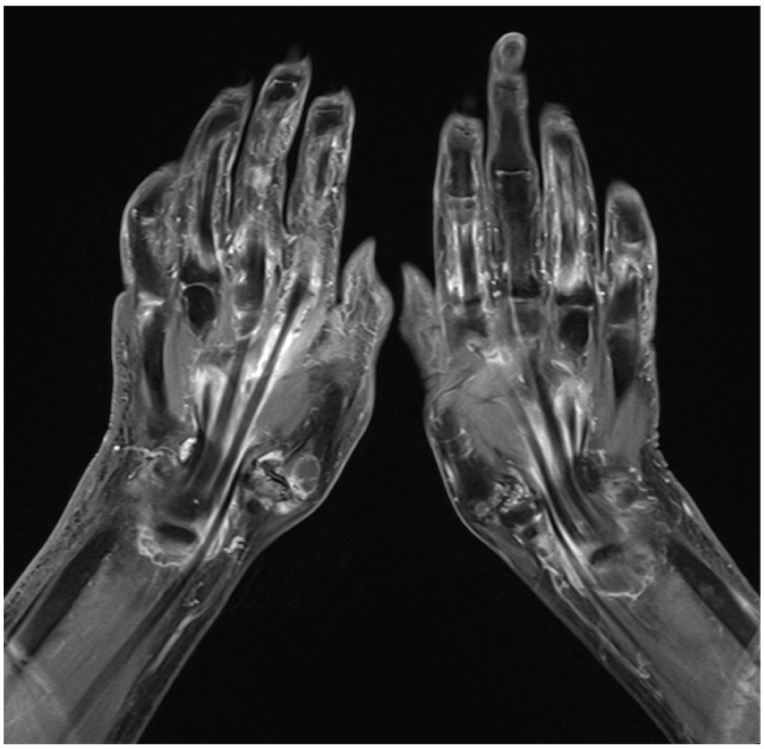

Fig. 3 MRI hands palmar-dorsal t1 tse Dixon coronary with contrast medium. Contrast-enhanced MRI of the hands shows bilateral tenosynovitis of the flexor tendons and enhancement in the carpus

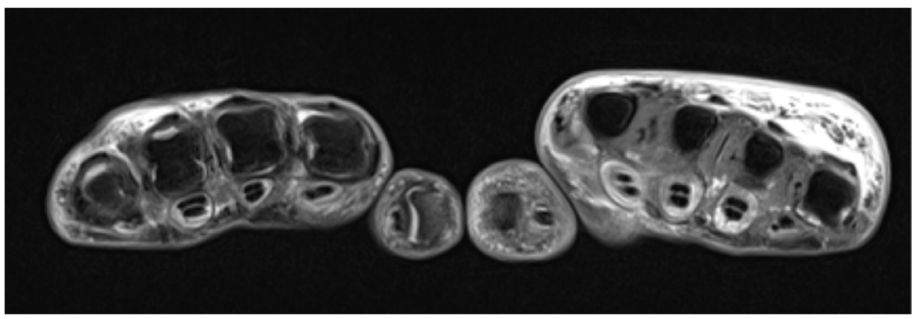

Fig. 4 MRI hand pd + t2 tse fs transversal with contrast medium. In contrast-enhanced MRI of the hands, the transverse section shows a right accentuated enhancement of the contrast medium of the dorsal hand. Furthermore, a tenosynovitis of the flexor tendons of both hands is visible

Results

The measures taken led to a rapid improvement of the symptoms, and the paresthesias in the area of the fingers disappeared. We considered the paresthesias to be symptomatic carpal tunnel syndrome in the context of carpal arthritis or tenosynovialitis of the flexor tendons. On re-presentation in our outpatient clinic after 3 months, the patient was symptom-free and in clinical remission under therapy with adalimumab 40 mg subcutaneous 1 × /2 weeks and prednisolone 3 mg daily. The swelling of the right dorsum of the hand was no longer evident.

Discussion

The clinical picture presented by our patient suggested R3SPE syndrome. In contrast to the medical data, our patient was female, had asymmetric manifestation in the clinical examination with right accentuated involvement of the upper extremity, and had a disease course of already 7 years. However, imaging studies showed a symmetrical involvement of both hands with the typical hallmark of tenosynovitis of both flexor and extensor tendons (right > left), constituting the pitting edema of the right hand. In appreciation of the medical record with established PsA, the clinical findings, and the literature,

where atypical RS3PE syndrome is described in the context of PsA [24, 25], we diagnosed an atypical RS3PE syndrome. Critically appraised with the new paradigm shift of RS3PE being a syndrome with autoinflammatory and autoimmune features in mind, one cannot clearly differentiate if this patient had only RS3PE from the start or if RS3PE developed on top of and in the context of the formerly diagnosed PsA.

In one case series, 9.6% of patients with PsA had RS3PE syndrome; in 18.8% of patients with this feature, it occurred as the first, isolated manifestation of PsA. In addition, the occurrence of pitting edema was associated with disease activity, and the upper extremities were predominantly asymmetrically affected in the study, in contrast to pitting edema in RA. The study hypothesized that edema in patients with PsA may be considered an atypical RS3PE syndrome because it is mainly unilateral and predominantly affects the upper extremities rather than the lower extremities [24].

VEGF and TNF-α have a role in the immunopathogenesis of RS3PE and early arthritis in RA as well as PsA, and these pro-inflammatory molecules may also contribute to development of atypical RS3PE syndrome in patients with PsA [26, 27].

Furthermore, an increase in VEGF has been described for both idiopathic and paraneoplastic RS3PE syndromes [28]. VEGF as a proangiogenic and permeability-increasing factor could mediate the clinically present subcutaneous edema as well as synovial hypervascularization with resulting synovitis [26]. This could be the reason that neoplasia, drugs, or various diseases trigger RS3PE syndrome [28, 29].

Therapy with csDMARDs was shown to be effective in the treatment of peripheral PsA but not in the treatment of RS3PE syndrome in the setting of PsA [30]. In general, bDMARDs have become an established therapy for the treatment of rheumatic diseases. A retrospective study and case reports have demonstrated the use of bDMARDs in the treatment of patients with PsA and pitting edema [24, 31, 32].

A therapeutic response to adalimumab could also be seen in this case report.

Finally, the genesis of the present RS3PE syndrome remains unclear:

- Years before the first manifestation, the patient suffered from a curatively treated cancer disease. In the medical data, case descriptions of present ovarian carcinoma and paraneoplastic occurrence of RS3PE syndrome are similar to this case [33, 34]. Poorer response to therapy and prolonged disease progression have been described in the setting of a paraneoplastic syndrome [23].
- Immediately before the appearance of the first symptoms, an immunization against TBE took place. Case reports of vaccination as a trigger of RS3PE syndrome can be found in the literature. However, these are limited to cases after immunization against SARS-CoV-2 and after intravesical application of Bacillus Calmette-Guérin [35–37]. An association with a previous TBE vaccination has not been described to date.
- In case of atypical manifestation with prolonged course of the disease and only the right dorsal hand affected, the RS3PE syndrome must be discussed as a differential diagnosis in the context of PsA even in the absence of skin and nail changes and non-fulfilment of the CASPAR classification criteria [24, 38].

Conclusion

In conclusion, RS3PE syndrome presents a unique constellation of symptoms that challenge its recognition and differentiation from other rheumatologic disorders. Nevertheless, in light of the recent paradigm shift classifying RS3PE as a syndrome with autoinflammatory and autoimmune features rather than a separate disease entity, the differentiation between RS3PE and RA or PsA appears to have decreased in relevance.

RS3PE typically manifests in elderly men with a peak at 70–79 years, marked by an abrupt onset of symmetric (teno)synovitis with the distinguishing hallmark of pitting edema involving the dorsal hands and feet, imparting a characteristic swollen appearance and is usually self-limiting after a few months of glucocorticoid treatment.

This case report highlights a rare presentation of an atypical RS3PE syndrome as contrary to the medical literature, the patient in this case is female, had an asymmetric manifestation with right accentuated involvement of the upper extremity, and had a disease course of already 7 years. Swift intervention with glucocorticoids has shown promising outcomes in symptom alleviation and improving patient quality of life, although long-term monitoring for potential adverse effects is crucial, as evidenced by this case in which the patient exhibits osteopenia and chronically elevated intraocular pressure with a history of glaucoma.

Considering the positive response seen in this patient as well as supporting evidence from medical literature, the initiation of adalimumab therapy may be deemed a viable option for achieving sustained clinical remission with minimal glucocorticoid dosing or potentially even in the absence of glucocorticoid therapy.

Abbreviations

ACPA	Anti-citrullinated protein antibodies
ANA	Antinuclear antibodies
ANCA	Antineutrophil cytoplasmic antibodies

CRP	C-reactive protein
CSA	Cross-sectional area
DMARD	Disease-modifying antirheumatic drug
ESR	Erythrocyte sedimentation rate
MCP	Metacarpophalangeal joints
MRI	Magnetic resonance imaging
PMR	Polymyalgia rheumatica
PsA	Psoriatic arthritis
RA	Rheumatoid arthritis
RF	Rheumatoid factor
RS3PE	Remitting seronegative symmetrical synovitis with pitting edema
TBE	Tick-borne encephalitis
TNFi	Tumor necrosis factor alpha therapy

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Authors' contributions
Conceptualization, NS and PK; data curation, formal analysis, funding acquisition, and investigation, NS and PK; methodology and project administration, UL; resources, UM-L and UL; software and supervision, UM-L; validation and visualization, NS; writing — original draft, NS and PK; and writing — review and editing, UM-L and UL.

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Availability of data and materials
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Declarations

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Consent for publication
Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Competing interests
The authors declare that they have no competing interests.

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