RS_3PE revisited: a systematic review and meta-analysis of 331 cases

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Abstract

Objective

Remitting seronegative symmetrical synovitis with pitting oedema (RS_3PE) syndrome is a rare inflammatory arthritis, characterised by symmetrical distal synovitis, pitting oedema of the hands and feet, absence of rheumatoid factor, and favourable response to glucocorticoids. The aim of our study is to further delineate the clinical and laboratory features, and response to treatment.

Methods

We performed a systematic electronic search of Medline, PubMed, EMBASE, ACR and EULAR databases for case reports, case series, and related articles of RS_3PE. Statistical analysis was done comparing categorical variables with Chi-square tests and frequencies of means via t-tests. Binary logistic regression analysis was performed to identify predictors of erosions, recurrence, malignancy and rheumatologic disorders.

Results

331 cases of RS_3PE were identified from 121 articles. RS_3PE was found in older patients (71±10.42 years) predominantly in males (n= 211, 63.36%), was symmetrical (n=297/311, 95.50%) involved the hands (n=294/311, 94.53%) A concurrent rheumatologic condition was reported in 22 cases (6.65%), and malignancy in 54 cases (16.31%). Radiographic joint erosions were found in 5.5%. Most patients responded to medium-dose glucocorticoids (16.12±9.5 mg/day). Patients with concurrent malignancy requiring non-significantly higher doses of prednisone (18.12 vs. 15.76 mg, p 0.304) and higher likelihood of recurrence of disease (OR 4.04, 95% CI 1.10–14.88, p=0.03).

Conclusion

The symptoms and unique findings that make up RS_3PE appear to represent a steroid-responsive disease that may be a harbinger of an underlying malignancy. More study is needed to understand the molecular origins of RS_3PE in order to determine whether it is a separate disease process. Patients with concurrent cancer tend to have more severe presentations and higher rates of recurrence.

Key words

RS_3PE, remitting seronegative symmetrical synovitis with pitting oedema, tenosynovitis

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Introduction

Remitting seronegative symmetrical synovitis with pitting oedema (RS$_3$PE) syndrome is a rare inflammatory arthritis, first described by McCarty *et al*. (1) in 1985 as a distinct form of late- onset seronegative rheumatoid arthritis (RA). Dr McCarty initially described the condition with the term "Boxing globe hand" to characterise the significant swelling seen. The nomenclature as he describes was deeply influenced by a very popular television programme of the 1970s, called TW$_3$ (This was the week that was) (2, 3), The French and Spanish authors have also referred to it as "Polyarthite aigué oedemateuse du sujet agé" (4) and "Sinovitis aguda edematosa del anciano" (5) respectively. It is characterised by abrupt onset of symmetrical distal synovitis, marked pitting oedema of the dorsum of the hands and/or feet, absence of rheumatoid factor (RF), and an excellent response to glucocorticoids which induce long term remission. Olive *et al*. proposed similar criteria but added an age cut-off of >50 years (6). Many additional case reports and reviews have been published to date describing varying clinical features and possible associations, including various solid organ tumours and haematological malignancies as a possible paraneoplastic syndrome. Also, rheumatologic diseases, including temporal arteritis, spondyloarthropathies (SpA), and Sjögren's syndrome (SS) and most frequently late-onset rheumatoid arthritis (LORA) and polymyalgia rheumatica (PMR) have also been described. However, these associations are not well established and confounded by various factors such as advanced age of onset and possibly publication bias. This paper attempts to gain a better understanding of the disease by performing a systematic review of all published cases of RS$_3$PE.

Search strategy and data collection

A systematic electronic search of Medline, PubMed, EMBASE, ACR and EULAR databases for case reports, case series, and related articles of RS$_3$PE from November 1985 to January 2014 was performed. The search terms used were: "arthritis, rheumatoid", "oedema", "synovitis", "RS$_3$PE", "remitting seronegative symmetrical synovitis with pitting edema" and "remitting seronegative symmetrical synovitis with pitting oedema". To minimise data duplication as a result of multiple reporting, we compared papers from the same author. Two authors (PK and SG) screened and retrieved reports and excluded irrelevant articles. Relevant data were extracted by two authors (PK and RP) and checked by another (MRA). Additional investigator (DP) participated in the review process when uncertainty about eligibility criteria arose. 331 cases were identified from 121 articles (Fig. 1). No language restriction was made and articles in 10 languages (English, Spanish, Dutch, French, German, Japanese, Chinese, Norwegian, Italian and Polish) were included. Language translation was done via translators proficient in the particular language and English; as well as google translator was used. Two foreign language articles (Arabic and French) were excluded as we could not translate the data in entirety. The demographic variables, clinical presentations, laboratory data, associated conditions, response to treatment and long term outcomes were noted**.** Categorical variables are expressed as percentage and continuous variables as mean ± standard deviation (SD). Continuous variables were compared using *t*-test and categorical variables using chi-squared tests. Independent *t*-tests were used to compare differences in total steroid dose per day, time to resolution, presence of malignancy and rheumatologic disorders with the presence or absence of erosions. Steroid doses were converted to equivalent dose of prednisone for comparison. Similarly, independent *t*-tests were performed to compare differences between ESR, time to onset and time to resolution to compare differences between those with or without malignancy and rheumatologic diseases. Mann-Whitney test was performed for CRP as the values did not have a normal distribution. Binary logistic regression analysis was performed to identify predictors of erosions, recurrence, malignancy and rheumatologic disorders in the study population. Statistical analysis was car-

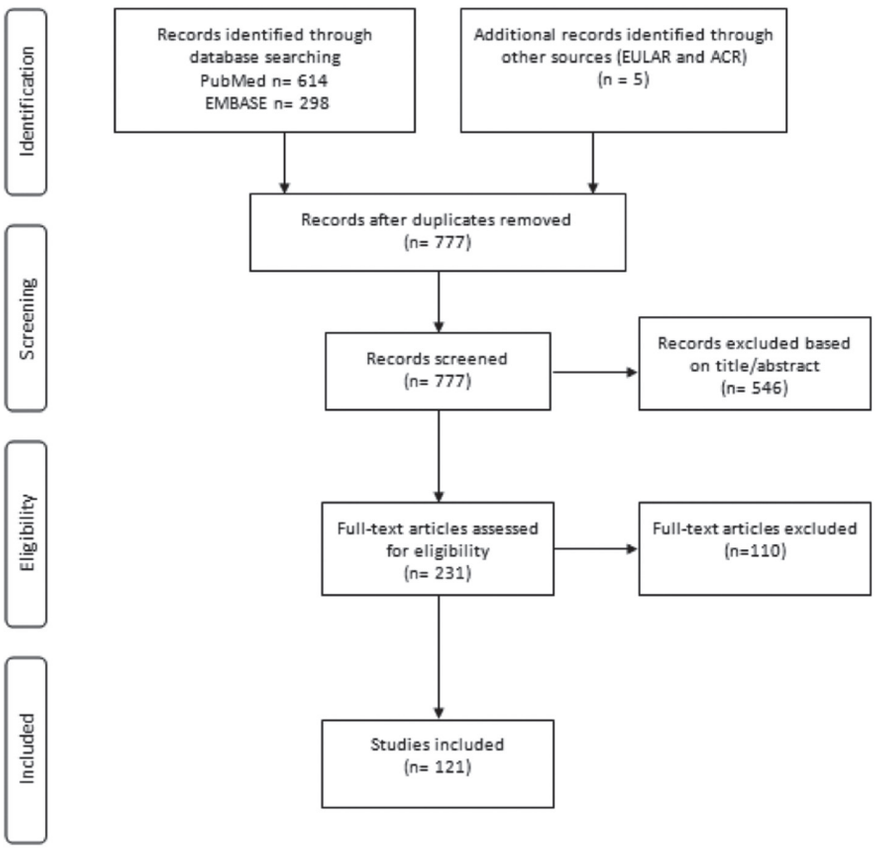

Fig. 1. Flow chart showing systematic literature search and study selection process.

ried out using Microsoft Excel 2007 (Microsoft Corporation, Redmond, WA) and IBM SPSS Statistics 20.0 (IBM Corporation, Armonk, NY). We used a 2-sided *p*-value of <0.05 to assess for statistical significance.

Results

Epidemiology and clinical features

331 cases of RS$_3$PE were identified from 121 articles in 10 languages with varying number of cases reported in the literature each year (Figure 2). RS$_3$PE was found predominantly in males (n=211, 63.4%) and the age at onset was 71±10.4 years. The pattern was symmetrical in most cases (n=297/311, 95.5%), with only a few reporting asymmetry (7-17). There was involvement of hands in 294/311 (94.6%) cases and feet in 140/311 (45%) cases. Site of involvement was not clear in 20 cases. Hand involvement was bilateral in most cases (n=282/294, 95.9%), with unilateral involvement noted in 12/294 (4.1%) cases (7-15). Involvement of bilateral feet were noted in 130/132 cases (98.5%) (16, 17). Other sites most commonly involved were the wrists (n=71/311, 22.83%), ankles (n=27/311, 8.7%) and shoulders (n=20/311, 6.4%). Fever was reported in 21 (6.3%) cases. Other frequently associated symptoms included anorexia, weight loss and fatigue (n=12, 3.62%), poor grip strength with inability to make a fist (n=23, 7%) and carpal tunnel symptoms (n=35, 10.57%). None of the cases reported presence of subcutaneous nodules.

Disease associations

An underlying rheumatologic condition was reported in 22 cases (6.65%) (Table I), the most common being polymyalgia rheumatica (PMR) (n=5, 1.51%), (18-22). Other conditions were crystal-induced arthritis (n=3, 0.9%), (23-25) Sjögren's syndrome (n=3, 0.9%) (26-28), 2 cases each (0.6%) of sarcoidosis (16, 29), giant cell arteritis, (21, 30) late onset peripheral spondyloarthropathy (LOPS) (18), and dermato-polymyositis (18, 31) (Table I). Among them, the most common were solid organ tumours (n=37, 11.18%) including genitourinary (n=17, 5.13%) (9, 32-45) (Table IIA), gastrointestinal (n=12, 3.62%) (6, 17, 32, 45-50), (Table IIB) followed by lung carcinoma (n=5, 1.51%) (17, 45, 51, 52), (Table IIC). Haematological malignancies occurred in 5% (n=17, 5.1%) (Table III).

Stepwise logistic regression analysis was done to identify independent predictors of the presence of concomitant malignancy (Table IVa) and rheumatologic disorder (Table IVb). Variables included were age, gender, presence of erosions, ESR, CRP, steroid dose, duration of treatment and time to resolution. By univariate analysis, female sex was the only variable significantly associated with the presence of malignancy (OR 0.42, CI 0.19-0.95, p=0.03). No significant predictors of concomitant rheumatologic disease were identified.

Medications were infrequently reported to be associated with the condition, with some of the notable ones being oral hypoglycemics (n=3, 0.91%) (41, 53) such as dipeptidyl peptidase-4 inhibitors (53), diuretics (n=2, 0.60%) (30, 48), benzodiazepines (30) and insulin therapy in a recent review (54). Associated antibiotics reported were rifampin (n=3, 0.60%) (55-57), ampicillin-sulbactam (14), trimethoprim/sulfamethoxazole (1), tobramycin (1) and clofazimine (57).

Laboratory parameters

Patients had a mean white cell count of 8,721±3896/mm^3, haemoglobin 12±1.9 mg/dl, elevated erythrocyte sedimentation rate (61.2±32.7mm/hr) and C-reactive protein (361.8±2136.6 mg/dl). Independent *t*-tests and Mann-Whitney tests were performed to explore differences between ESR and CRP respectively in cases with and without the presence of haematological or rheumatologic diseases did not reveal statistical difference. Rheumatoid factor (RF) was negative in most cases, with only six RF-positive cases (n=6/238, 2.52%) (26, 32, 58-61). Antinuclear antibody (ANA) was weakly positive in 13/189 (6.88%) cases reporting it (9, 26, 31, 37, 62-67). None of the cases (19 cases where it was checked) reported anti-citrullinated protein antibody (ACPA) positivity. Vascular endothelial growth factor (VEGF) was found

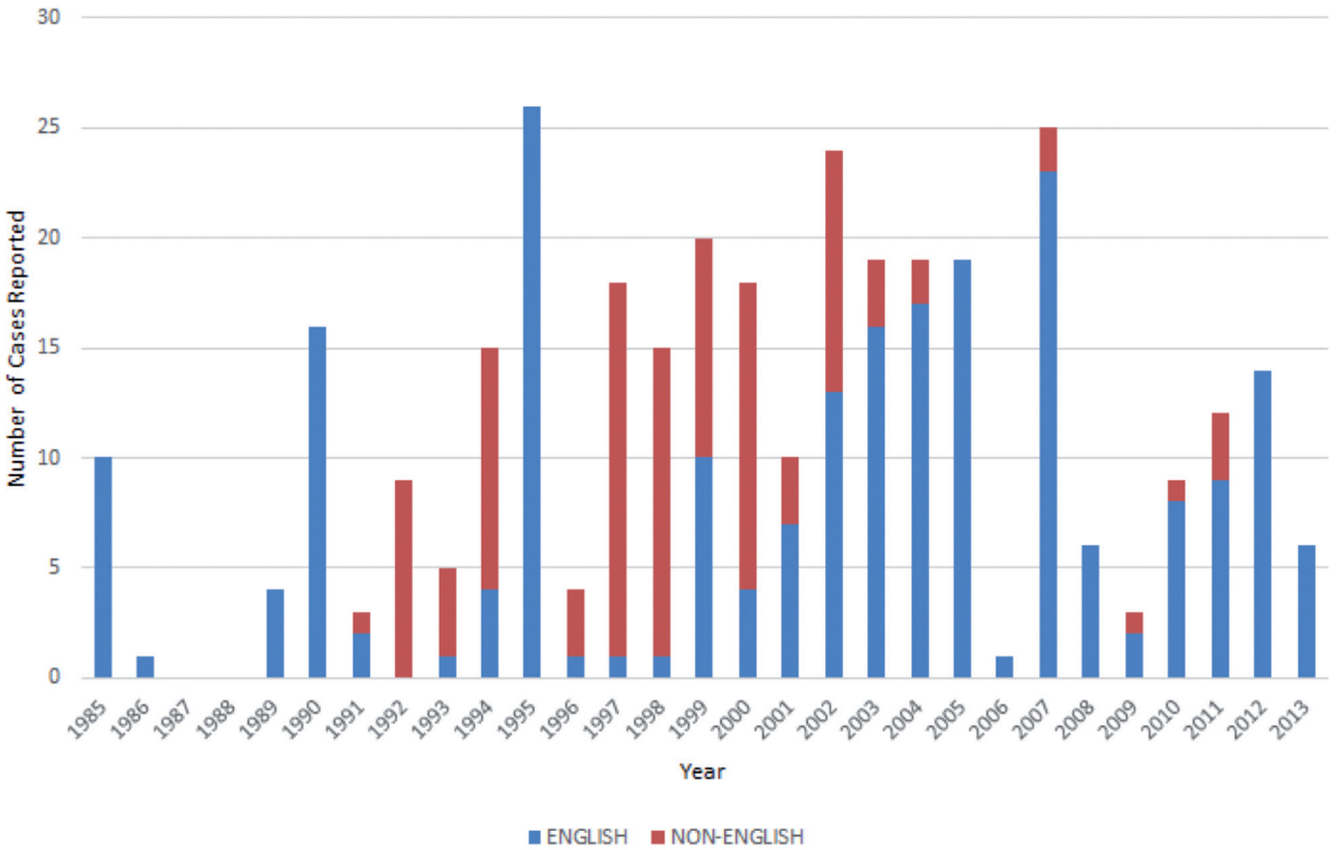

Fig. 2. Trend of RS3PE cases reported in the literature per year (1985–2013).

to be significantly elevated (2-3 times above normal) in the 5 cases reporting it, but was not checked in others. Most common human leukocyte antigen (HLA) associations noted were HLA-A2 (n=41/117 cases reporting it, 35%), HLA-B7 (n=38, 32.5%).

Radiographic features

Radiographic joint erosions were found in 4.7% of cases (n=6/128) (8, 24, 68, 69), out of which 3 cases (2.3%) were associated with an underlying crystal induced arthropathy (CIA) (23–25). There were too few reported erosions (n=6) for any meaningful analysis of associations of cancer. Sixty-six cases reported associated tenosynovitis. The most common imaging modality used was ultrasound and magnetic resonance imaging (MRI) of the affected part (n=20, 6%).

Treatment

Glucocorticoid was the most commonly used treatment (n=276/331, 83.4%), with most patients responding to a low initial dose (16.1±9.4 mg/day). Non-significantly higher doses of steroids were used in cases with concomitant malignancy as compared to those without malignancy (18.1 *vs*. 15.8mg, p=0.13) or rheumatologic disorder (18.3 *vs*. 16.0, p=0.3). The most commonly used corticosteroid was prednisone (n=116/276, 42.03%) followed by prednisolone (n=89/276, 32.25%), NSAIDs were frequently given in the acute setting in addition to steroids (n=106, 32%). Other therapies used were hydroxychloroquine (n=24, 7.3%), colchicine (n=4, 1.2%) and unspecified disease-modifying anti-rheumatic drugs (DMARDs) (n=9, 2.7%) with variable efficacy. Mean time to resolution was 133±123 days, with most cases starting to show improvement within a week.

Recurrence after treatment was reported in 29/331 cases (8.76%), out of which 8 cases had concurrent malignancy (33-36, 42, 70, 71). Binary logistic regression to determine predictors of recurrence was significant for presence of malignancy at diagnosis (OR 4.04, 95% CI 1.01–14.9, p=0.031) and solid organ tumours (OR 6.74, 95% CI 1.43–31.8, p=0.010) (Table IIC).

Discussion

Epidemiology and clinical features

Our review shows that RS$_3$PE as represented in the literature does indeed have a predominantly older age of onset (71±10 years), supporting Olive et al's assertion that the age cut-off of >50 years might effectively be raised upward (72).

Based on our review, we suggest the following criteria for diagnosis: 1) abrupt onset, 2) marked pitting oedema of mostly hands (and/or feet), 3) age of onset ≥60 years, 4) good response to short course of medium dose steroids (10–20 mg), 4) seronegative for RF and ACPA, and 5) absence of radiographic joint erosions. Ultrasound evidence of extensor tenosynovitis of wrist and metacarpal heads may supplement the diagnosis, if this is found to be a distinguishing feature in future cases. However this would require further study.

Disease associations

Although there have been many case reports and some retrospective studies in RS$_3$PE, this disease remains poorly

Table I. Baseline characteristics of RS$_3$PE cases with concurrent rheumatologic disease

First author, year	Age/Sex	Concurrent rheumatologic condition	WBC (/mm^3)	Presence of erosions on imaging	ESR (mm/hr)	CRP (mg/dl)	ANA titer	RF titer	Equivalent initial corticosteroid dose (mg/day)	Duration of treatment (days)	Time to resolution (days)	Recurrence
Berthier, 1998 (18)	84/M	PMR	…	...	40	1.7	Negative	Negative	...	90	...	...
Berthier, 1998 (18)	65/M	LOPS	…	...	96	6.3	Negative	Negative	10	240	...	...
Berthier, 1998 (18)	63/M	LOPS	…	...	50	6.1	Negative	Negative	...	870	...	...
Berthier, 1998 (18)	71/M	Dermato-polymyositis	…	...	27	0.3	Negative	Negative	10	1830	...	...
Choi, 2003 (26)	35/F	SS	4330	...	27		1:320, speckled pattern	54.4 IU/ml	20	...	...	...
Cobeta Garcia, 1999 (27)	66/M	SS	…	...	116			Negative	15	360	...	...
Colnot, 2004 (66)	81/M	SLE	560*	No	12	0.1	1:1200, homogenous	Negative	...	...	...	...
Dejaco, 2008 (29)	32/M	Sarcoidosis	…	No	20	9.7	Negative	Negative	...	...	...	...
Diez Porres, 2002 (69)	74/F	Psoriatic arthropathy	2980	Yes	41	0.98	Negative	Negative	10	180	28	At 5 mo, few days after stopping prednisone
Gomez huelgas, 2002 (30)	88/F	GCA	…	No	65	95.3	Negative	Negative	10	60	7	...
Hakozaki, 2013 (23)	76/M	CIA	10300	No	115	17.1	…	Negative	...	7	4.00	...
Koeger, 1995 (84)	63/M	AS	…	No	90	19700	…	…	20	...	21	
Matsuda, 2004 (16)	62/F	Sarcoidosis	…	...	92	5.36			30	...	...	...
Matsuda, 2005 (19)	82/F	PMR	…	...	24	11.1	Negative	Negative	20	...	...	RS$_3$PE associated with PMR at the onset of the disease but only PMR symptoms at relapse, time to relapse not mentioned
Paira, 2002 (46)	64/F	PAN	…	No	18	…	…	Negative	10	420	...	...
Palazzi, 2003 (24)	76/M	CIA	…	Yes	47	4.4	Negative	Negative	...	10	...	...
Salam, 2008 (20)	67/M	PMR	…	No	70	100	Negative	Negative	7.5	...	56	...
Schaeverbeke, 1995 (21)	66/M	PMR associated with biopsy proven GCA	…	...	110	…	Negative		10	...	300	...
Shan Sei Fan, 1999 (22)	85/F	PMR	…	...	39	...	…	Negative	...	...		...
Sugisaki, 2008 (25)	70/M	CIA	…	...	...	21.6	Negative	Negative	20	...	2	...
Takeda, 2010 (31)	73/F	Dermatomyositis	9.54	No	121	8.2	1:160, discrete speckled	Negative	20	...	90	...
Tanaka, 1997 (28)	51/F	SS	5990	...	...	19.3	Negative	Negative	40	...	...	During prednisone taper, time to relapse not mentioned

* lymphopenia.
ANA: antineutrophil antibody; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; F: female; CIA: crystal-induced arthropathy; GCA: giant cell arteritis; hr: hour; IU: international units; LOPS: late-onset peripheral spondyloarthropathy; M: male; mg: milligrams; ml: milliliters; mm: millimeters; PAN: polyarteritis nodosa; PMR: polymyalgia rheumatica; RF: rheumatoid factor; AS: ankylosing spondylitis; RS$_3$PE: remitting symmetric seronegative synovitis with pitting oedema; SLE: systemic lupus erythematosus; SS: Sjögren's syndrome; WBC: white blood cell.

characterised. A central question remains whether RS$_3$PE is a distinct clinical entity, a variant of other rheumatologic diseases, or a paraneoplastic syndrome. Some reports in the past suggested that RS$_3$PE is a syndrome that may represent late onset of some rheumatic diseases, such as seronegative RA, spondyloarthropathies, PMR and SS (73). Almost 50% of these were found to be associated with rheumatologic diseases as per previous reviews (37). The major difficulty in the interpretation of the results lies in the fact that there are no definite criteria for the diagnosis of this condition. We included studies diagnosed as RS$_3$PE as per the author's judgment. However, there were some that did not fulfill the McCarty criteria, with few being unilateral, presence of RF and erosions noted in the radiograph. Whether these cases represent the same entity is a matter of debate. Unlike what has been described in the literature, we found that only a limited percentage of cases had an associated concomitant rheumatologic disorder (4.23%). Publication bias and limited follow-up periods in most cases makes it difficult to interpret these findings. The absence of subcutaneous nodules, RF, radiographic erosions and good response to low dose steroids with complete resolution makes late-onset rheumatoid arthritis (LORA) a less likely possibility as an explanation

Table IIA. Baseline characteristics of RS$_3$PE cases with concurrent solid organ tumours – genitourinary malignancy.

First author, year	Age/Sex	Malignancy	Erosion on imaging	ESR (mm/ hr)	CRP (mg/ dl)	WBC	Initial equivalent steroid dose (mg/day)	Other Rx	Rx (days)	TTR (days)	Recurrence	Outcome
Bruscas Izu, 2013 (42)	72/F	TCC Bladder	No	120	1.1	…	10	HCQ 200 mg/d	…	90	…	Tenosynovitis and oedema resolved with normalisation of ESR and CRP at 1 month and resolution by 90 days
Bucaloiu, 2007 (37)	80/M	Low grade bladder TCC diagnosed 13 months after diagnosis of RS$_3$PE	No	25	…	…	17.5	None	195	…	…	Complete remission
Bucaloiu, 2007 (37)	76/M	Prostate Ca diagnosed one month after diagnosis if RS$_3$PE status post anti-androgenic therapy	No	8	…	…	17.5	…	…	…	No	…
Dudler, 1999 (9)	78/M	Prostate adenoca diagnosed 8 months after remission	No	64	8800	…	15	…	…	…	No	Complete resolution
El Mahou, 2006 (35)	73/M	Grade 3 bladder ca, status post endoscopic resection and weekly intravesical BCG administration	…	80	70	…	…	Ketoprofen and INH, BCG instillation stopped	…	…	…	Complete resolution with no relapse at 1 month follow-up
Finnell, 2000 (32)	72/M	History of Colon Ca and Prostate Ca	…	45	…	…	15	…	175	…	…	Rapid and complete resolution with steroid
Juncadella, 2003 (43)	85/M	Renal cell carcinoma	…	110	109	…	30	…	…	…	…	Relapse 12 weeks after surgery and prednisone re-started
Marto, 2010 (33)	74/M	Adenoca of prostate diagnosed via prostate biopsy immediately after RS$_3$PE was diagnosed	No	130	15.51	…	20	Diclofenac 150 mg/day, oral, anti-androgenic therapy	…	…	…	Remission after corticosteroid and anti-androgenic therapy
Moran Blanco, 2003 (44)	78/M	Bladder TCC and MM	…	8	…	…	…	Melphalan 8 mg/m^2/day	540	…	…	…
Tunc, 2004 (34)	74/M	Prostate adenocarcinoma, Gleason score 7	…	79	19	…	10	Anti-androgen therapy	90	90	… 1	Oedema resolved after 0 days but arthralgia persisted
Tunc, 2004 (34)	70/M	History of prostate carcinoma, high grade with bone metastasis, status post TURP and bilateral orchiectomy, diagnosed 3 months earlier to RS$_3$PE onset	…	…	…	…	10	NSAID, Zoledronic acid, anti-androgen	14	…	…	Oedema and pain resolved 2 weeks later
Vinci, 2001 (39)	69/F	Right ovarian carcinoma FIGO stage IIb status post debulking diagnosed at 7 months relapse	…	120	108	…	20	Chemotherapy	…	30	…	Resolved rapidly over 6 months with steroids, relapse at 7 months, completely resolved 2 months after tumour debulking
Yalbuzdag, 2013 (15)	76/M	Prostate adenocarcinoma, status post radical prostatectomy diagnosed 2 years prior to RS$_3$PE diagnosis	No	32	12	…	20	…	…	14	…	Oedema and pain resolved over 2 weeks, rapid response to steroid with no relapse at 2 months
Mouly, 2001 (36)	65/M	Moderately differentiated TCC of bladder plus six weekly BCG administration	No	91	24	13300	40	Ketoprofen 100 mg IV once daily + Morphine sulfate 30 mg oral twice daily for 3 days, followed by indomethacin 50 mg TID	…	…	Yes	Did not respond to initial prednisolone 30 mg/day, No relapse at 4 months
Okumura, 2012 (40)	82/M	Prostate carcinoma (diagnosed 10 years ago) with bone metastasis	…	88	9.82	8750	30	…	…	…	…	Death after 1 year from metastatic prostate ca
Origuchi, 2012 (45)	81/M	Prostate ca	…	55	6.37	7410	5	…	73	…	No	No relapse, complete resolution with prednisolone

BCG: bacillus Calmette-Guérin; Ca: cancer; CRP: C-reactive protein; dl: deciliter; ESR: erythrocyte sedimentation rate; F: female; GU: genitourinary cancers; HCQ: hydroxychloroquine; hr: hour; INH: isoniazid; M: male; mg: milligrams; mm: millimeters; MM: multiple myeloma; RS$_3$PE: remitting symmetric seronegative synovitis with pitting oedema; Rx: treatment; TCC: transistional cell cancer; TTR: time to resolution; WBC: white blood cellll.

Table II B. Baseline characteristics of RS_3PE cases with concurrent solid organ tumours – gastrointestinal malignancy.

First author, year	Age/Sex	Type of malignancy	Presence of erosions on imaging	ESR (mm/ hr)	CRP (mg/ dl)	WBC (/mm^3)	Initial cortico-steroid dose (mg/day)	Other medications	Rx (days)	TTR (days)	Recur-rence	Outcome
Cantini, 1999 (76)	46/M	Sigmoid adeno Ca diagnosed at the time of presentation	…	48	2.6	…	12.5	Indomethacin 150 mg/day, surgical resection of adenocarcinoma	60	…	…	Poor response to steroid and NSAID. Gradual resolution 10 days after surgical resection
Ethiopia, 1999 (50)	82/F	Metastatic gastric adenocarcinoma diagnosed at the time of diagnosis of RS_3PE	No	63	…	13400	20	…	14	…	…	Died after 4 months due to massive PE
Finnell, 2000 (32)	72/M	History of Colon Ca and Prostate Ca	…	45	…	…	15	…	175	…	…	Rapid and complete resolution with steroid
Nakashima, 1999 (47)	69/M	HCC, (moderately differentiated status post anterior segmentectomy of liver) diagnosed at the time of diagnosis of RS_3PE	No	52	4.9	10500	20	…	…	7	…	Rapid resolution with prednisolone within 48 hours
Olive, 1997 (6)	…	Rectal Ca- remote	…	…	…	…	…	…	…	…	…	…
Origuchi, 2012 (45)	74/M	Stomach Ca	…	79.1	11.3	6500	20	…	51	…	No	Good response to prednisolone, No relapse
Origuchi, 2012 (45)	73/M	Rectal Ca	…	108	12.35	17900	30	…	45	…	No	Good response to prednisolone, No relapse
Origuchi, 2012 (45)	79/M	Colon Ca	…	98	8.7	5800	20	…	36	…	No	Good response to prednisolone, No relapse
Origuchi, 2012 (45)	87/M	Stomach Ca	…	41	10.69	6100	20	…	30	…	No	Good response to prednisolone, No relapse
Paira, 2002 (46)	68/M	Rectal adeno Ca diagnosed 2 months before diagnosis of RS_3PE	…	60	…	…	10	…	…	…	…	Poor response to steroid, Complete resolution following colectomy
Ramos Soria, 2003 (41)	73/M	Prostate adeno Ca , Gleason score 7	…	30	…	…	…	Flutamide	…	…	…	Relapse after 10 months
Tada, 1997 (48)	80/F	Gastric adenoca	No	135	10.1	6900	…	Loxoprofen, intra-articular Triamcinolone injection	…	…	…	Poor response to steroids, complete resolution following gastrectomy
Cantini, 1998 (49)	75/M	Ca head of pancreas without metastasis, diagnosed at the time of RS_3PE diagnosis	No	108	8.9	…	…	…	…	…	…	No remission with initial NSAIDs, complete resolution following surgical resection with no relapse at 4 months

Ca: cancer; CRP: C-reactive protein; dl: deciliter; ESR: erythrocyte sedimentation rate; F: female; FIGO: International Federation of Gynaecology and Obstetrics; GU: genitourinary cancers; HCC: hepatocellular carcinoma; hr: hour; M: male; MM: multiple myeloma; mg: milligrams; mm^3: cubic-millimeter; NSAID: non-steroidal anti-inflammatory drug; RS_3PE: remitting symmetric seronegative synovitis with pitting oedema; Rx: treatment; TCC: transistional cell cancer; TTR: time to resolution; WBC: white blood cell.

for these symptoms, but whether this represents a manifestation spectrum of RA remains unknown. Similarly, very few patients had HLA-DRB1 or HLA-B27, unlike LORA or LOPS cases respectively. Imaging modalities such as ultrasound and MRI may also be helpful, as RS_3PE and PMR demonstrate non-synovial pathology with prominent changes adjacent to the joint capsule in contrast to RA (74). Some authors also suggest that subacromial and subdeltoid bursitis are more commonly associated with PMR involving the shoulder joint; however these findings are yet to be validated (75).

There has also been a growing debate if RS_3PE represents a variant of PMR (76). Although both of these do share common features such as acute onset in the elderly, excellent response to medium-dose steroids and non-synovial pathology on imaging. However, those that believe that this is a distinct entity note that RS_3PE is more common in males and there is involvement of distal extremities with imaging commonly

Table II C. Baseline characteristics of RS$_3$PE cases with concurrent solid organ tumours – lung carcinoma and others.

First author, year	Age/Sex	Type of malignancy	Presence of erosions on imaging	ESR (mm/ hr)	CRP (mg/ dl)	WBC (/mm^3)	Initial cortico-steroid dose (mg/day)	Other medications	Rx (days)	Time to resolution (days)	Recur-rence	Outcome
Lung carcinoma												
Allain, 2010 (52)	60/M	Adeno Ca of Lung and lymphangitic carcinomatosis	…	60	10.7	…	…	Chemotherapy	…	…	…	…
Cantini, 1999 (17)	78/M	Undifferentiated lung carcinoma diagnosed at the time of diagnosis of RS$_3$PE	...	98	1.8	…	50	…	…	…	…	Poor response to steroid, died 1 month later
Origuchi, 2012 (45)	80/M	Lung carcinoma	…	…	10.59	8230	5	…	24	…	No	Good response to prednisolone, No relapse
Origuchi, 2012 (45)	83/M	Lung carcinoma	…	89	3.96	3900	20	…	396	…	Yes	Good response to prednisolone, relapse over subsequent months
Terada, 2004 (51)	61/M	Lung carcinoma stage Ia	…	38	10.2	…	…	…	…	…	…	…
Other malignancies												
Olive, 1997 (6)	…	Breast carcinoma, remote	…	…	…	…	…	…	…	…	…	…
Origuchi, 2012 (45)	78/F	Breast carcinoma	…	…	11.09	7000	20	…	135	…	No	Good response to prednisolone, No relapse
Paira, 2002 (46)	62/M	Fibrohistiocytoma diagnosed 8 months after RS$_3$PE onset	…	60	…	…	16	Chemotherapy	…	…	Yes	Poor response to steroid
Cantini, 1999 (17)	59/M	Undifferentiated carcinoma (seen in CT guided biopsy from an osteolytic lesion of pelvis) diagnosed 2 months after diagnosis of RS$_3$PE	…	84	…	…	12	…	…	…	…	Died 2 months after diagnosis of Ca

Ca: cancer; CRP: C-reactive protein; CT: computed tomography; dl: deciliter; ESR: erythrocyte sedimentation rate; F: female; FIGO: International Federation of Gynaecology and Obstetrics; GU::genitourinary cancers; HCC: hepatocellular carcinoma; hr: hour; M: male; MM: multiple myeloma; mg: milligrams; mm^3: cubic-millimeter; NSAID: non-steroidal anti-inflammatory drug; RS$_3$PE: remitting symmetric seronegative synovitis with pitting oedema; Rx: treatment; TCC: transistional cell cancer; TTR: time to resolution; WBC: white blood cell.

showing extensor tenosynovitis (77). This is in contrast to PMR, which is more common in females and involves the proximal extremities. Similarly, the recurrence of RS$_3$PE was reported in only a few cases, while most sustained remission off the prednisone in contrast with PMR, where the disease has a more protracted course and frequent flares while trying to taper prednisone. In spite of these striking differences, the differential diagnosis is still broad, and includes LORA, LOPS, PMR, CIA, amyloid arthropathy, thyroid arthropathy, paraneoplastic syndrome, early scleroderma and mixed connective tissue disease.

Our study found a significant number of cases with a concurrent malignancy (16.01%), especially solid organ tumours (11.18%) involving the genitourinary and gastrointestinal tract. The patterns of reported malignancies however are different from the ones related to rheumatoid arthritis or other rheumatologic conditions where a high rate of lymphoma and lung carcinoma have been reported (78). This may be a further clue that in fact RS$_3$PE is likely a distinct entity. Although some authors have pointed toward RS$_3$PE as a paraneoplastic syndrome linked to haematological malignancies, our review noted a higher incidence of solid organ tumour associations, suggesting that this paraneoplasic association should be broadened. The cost-effectiveness of aggressive cancer screening for patients with RS$_3$PE compared to age-appropriate screening will require further research, but physicians diagnosing this rare disorder should be aware of these associations. Although scarce reports of drug associated RS$_3$PE, mostly antibiotics and oral hypoglycemics have been reported, it is unclear whether these are related to causation or act as triggers for the genetically- predisposed individuals.

Laboratory and radiological findings

Laboratory findings include a normal white cell count with varying degrees of anemia of chronic disease with elevated acute phase reactants but low or absent ANA titers (rarely ≥1:80). Although a few cases were weakly RF positive, we question if these were pure RS$_3$PE cases. We propose that RF -positive cases should be categorised

Table III. Baseline characteristics of RS_3PE cases with concurrent haematological malignancy.

First author, Year	Age/Sex	Type of malignancy	ESR (mm/hr)	CRP (mg/dl)	WBC (/mm^3)	Equivalent steroid dose (mg/day)	Other therapies	Rx (days)	Outcome
Beyne-Rauzy, 2001 (85)	72/M	MDS	…	…	…	20	…	…	…
Bucaloiu, 2007 (37)	67/F	History of NHL, remote	54	…	…	17.5	DMARD	150	Relapse
Bucaloiu, 2007 (37)	80/M	NHL diagnosed 2 months after diagnosis of RS_3PE	58	…	…	17.5	DMARD	420	Complete resolution
Chiappetta, 2005 (70)	82/M	AML diagnosed 3 months after diagnosis of RS_3PE	122	…	6800	10	Chemotherapy	…	Rapid resolution in 1 week with steroids, recurrence with attempted taper
Cobeta Garcia, 1999 (86)	72/F	CLL	12	5	…	15	…	210	Relapse
Ekenel, 2000 (71)	67/M	CLL stage 4 diagnosed at the time of diagnosis of RS_3PE	28	…	18,000	16	Chemotherapy	…	Dramatic resolution within 1 week, no relapse; died 8 months later from sepsis
Garcia-Cortes, 2003 (87)	72/M	CLL diagnosed 4 years prior to RS_3PE diagnosis	…	…	39,700	…	…	…	Initial resolution with 2 weeks of steroid, relapse at 3 months after taper
Hernandez-Beriain, 1996 (88)	88/M	Myelodysplastic syndrome 2 months before diagnosis of RS_3PE	60	…	18,000	15	…	…	Complete resolution following steroid, no recurrence at 8 months
Moran Blanco, 2003 (44)	78/M	Bladder TCC and MM	8	…	…	…	Melphalan 8 mg/m^2/day	540	No recurrence
Olive, 1997 (6)	67/F	Angiocentric T cell lymphoma shortly after polyarthitis	32	...	5,680	...	...	...	Poor response to glucocorticoids, 8 mo evolution
Olive, 1997 (6)	71/ --	T cell Lymphoma	34	80.5	8,600	18	…	…	Good response to glucocorticoids initially, developed generalised lymphadenothay 15 days later
Olive, 1997 (6)	69/F.	Myelodysplastic syndrome 4 months after RS_3PE onset	67	41	...	8	MTX added after	...	Good response to recurrence glucocorticoids initially, but recurrence
Paira, 2002 (46)	75/M	Myelodysplastic syndrome 11 months after RS_3PE onset	60	…	…	12	Erythropoetin, androgens	…	Poor response to steroids
Paira, 2002 (46)	60/M	NHL 16 months after RS_3PE onset	60	…	…	…	Chemotherapy, Cyclophosphamide	…	Poor response to steroids, complete response following cancer therapy
Sayarlioglu, 2003 (89)	63/F	NHL diagnosed at the time of diagnosis of RS_3PE	54	68.8	normal	15	Chemotherapy	21	Dramatic resolution within 2 days, no relapse at 6 months
Sekhon, 2010 (90)	81/M	CLL diagnosed at the time of RS_3PE diagnosis	…	42.2	…	15	…	360	Complete resolution at 3 weeks, no recurrence at 12 months
Lilleby, 1997 (91)	81/M	Multiple myeloma	46	…	…	10	Oral Gold (auranofin) 3 mg BID	…	No recurrence at 20 months
Yamasaki, 2002 (92)	67/…	Malignant lymphoma	…	11.3	11,600	15	Ioxoprofen 180 mg/day, Diclofenac	…	…

AML: acute myeloid leukaemia; CLL: chronic lymphocytic leukaemia; CRP: C-reactive protein; DMARD: disease-modifying anti-rheumatic drug; ESR: erythrocyte sedimentation rate; F: female; M: male; mg/day: milligrams per day; MDS: myelodysplastic syndrome; NHL: non-Hodgkin lymphoma; RS_3PE: remitting symmetric seronegative synovitis with pitting oedema; Rx: treatment; WBC: white blood cell.

as atypical RS_3PE and these followed closely over time for development of other rheumatologic disorders. ACPA was not reported to be positive in any of the cases. One of the recently published cases (published after our search reported ACPA positivity; however the case seemed to be related to RA and not a true RS_3PE syndrome (79). Serum VEGF levels may be associated with its pathogenesis and it might be useful for the diagnosis and monitoring of disease activity (80). Our study shows a higher prevalence of HLA- A2 predominance like one of the previous studies (21), followed by HLA-B7 (1, 60). HLA-DRB1 commonly associated with RA was not seen and HLA- B27 associated with LOPS (81) respectively was rare. Radiographic joint erosions were very rare (1, 6, 77). Imaging modalities such as ultrasound (8) and magnetic resonance imaging (76) were helpful in visualising subcutaneous oedema and extensor tenosynovitis (unlike the original description by McCarty describing involvement of flexor tendons of the hands) which seem to be the hallmark of the condition. Moreover, tenosynovitis seems to parallel the

disease activity as well as response to corticosteroids. Whether ultrasound can be used for diagnosis and monitoring of disease activity and response is a matter for further study. There is very scarce data concerning synovial fluid. Cell count is variable, usually less than 3,000 /mm^3 with polymorphonuclear predominance in the few reported cases (82). Synovial biopsy yielded a non-specific synovitis (60).

Management and prognosis

Most patients had an excellent response to medium-dose prednisone, mostly within a week (46, 81). However, patients with concurrent malignancy were found to resistant to medium-dose steroids (34, 46, 77) and more likely to have a recurrence (33-36, 42, 70, 71). In most cases, steroids could be tapered off after duration of 2-3 months. Uncomplicated cases of RS$_3$PE were found to have excellent prognosis with recurrences reported in only a few cases. A follow-up study of RS$_3$PE patients 6 years later showed that majority of patients were asymptomatic and not any therapy. The patients who were on NSAIDs, glucocorticoids and DMARDs were found to have other concomitant rheumatologic disorders such as seronegative RA, PMR and systemic sclerosis (83).

Limitations

Our study has several limitations. First, this was a based on a collection of reported cases from the literature, so publication bias cannot be excluded (though we did include abstracts from regional meetings and multiple languages). Second, we included cases diagnosed by the clinical judgment of the physicians and accepting editors, but there was no way for us to verify these diagnoses. Since most case reports do not have a long follow-up period, the long-term outcome of these patients and development of another rheumatologic disorder or malignancy over time could not adequately be studied.

Conclusion

It remains unclear whether RS$_3$PE is a distinct entity rather than a subset of other rheumatologic diseases or a paraneoplastic syndrome. However, clinicians should be aware that patients with concurrent cancer tend to have more severe presentation and resistance to medium-dose steroids. The cost effectiveness of aggressive cancer screening for patients with RS$_3$PE compared to age-appropriate screening will need further research. RF positive cases should be categorised as atypical RS$_3$PE and followed closely over time for development of other rheumatologic disorders. Some authors believe that serum VEGF levels may be associated with its pathogenesis and it might be useful for the diagnosis and monitoring of disease activity; this is an important avenue for future research. An international disease registry may be beneficial in this regard. Recognition of this condition is important as uncomplicated cases of RS$_3$PE usually have an excellent prognosis and long term use of glucocorticoids or immunosuppressive agents should be discouraged.

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