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Original Research Article

Medium to Low Dose Prednisolone Therapy (MLDPT) for 'Remitting Seronegative Symmetrical Synovitis with Pitting EDEMA' (RS3PE) on Novel Anticancer Therapy. Onco-Rheumatological Case Series, Systematic Review And Meta-Analysis

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Conflict of interest: Nil

Abstract

Aim of the work: To report series of 'remitting seronegative symmetrical synovitis with pitting edema' (RS3PE) in oncology setting with novel anticancer therapy and systematic review of treatment of this entity.

Patients and Methods: Retrospective data collection of patients who had RS3PE after starting novel anticancer therapy with tyrosine kinase inhibitors(TKI) or immune checkpoint inhibitors in last one year. Systematic review of previous case reports with similar presentation and meta-analysis of treatment given was done.

Results: Total 4 cases (2 males and 2 females) presenting as RS3PE with background of malignancy were detected. Three patients had metastatic renal cell carcinoma (RCC) and were on treatment with pazopanib. One patient had head and neck squamous cell carcinoma (HNSCC) and was on treatment with nivolumab. All patients responded to medium to low dose prednisolone therapy (MLDPT). None of the patients had long term sequelae. One of the patients had to discontinue inciting therapeutic agent temporarily, not due to arthritis but due to underlying co morbidities.

Conclusion: MLDPT is effective therapeutic strategy in RS3PE with malignancies on novel anticancer therapy. With systematic review of literature we tried to throw light on causation, mechanism, profile, natural history and therapeutic significance. We have also reviewed efficacy of various drugs used in treatment of RS3PE as per reported literature.

Keywords: RS3PE, MLDPT, Seronegative, Symmetrical, Synovitis, Pitting.

Abbreviations: RS3PE: remitting seronegative symmetrical synovitis with pitting edema, MLDPT: medium to low dose prednisolone therapy, VEGF: vascular endothelial growth factor, RCC: renal cell carcinoma, HNSCC: head and neck squamous cell carcinoma, NSAID: non-steroidal anti-inflammatory agent, SSZ: sulphasalazine, HCQ: hydroxychloroquine, CsDMARD: conventional synthetic disease modifying antirheumatic drugs, bDMARD: biological disease modifying antirheumatic drugs.

Introduction

Immunotherapy (checkpoint inhibitors) and angiogenesis inhibitors (against vascular endothelial growth factor/ VEGF) are new generation agents which are thought to be associated with effects and side effects of different spectrum than conventional chemotherapy. So they are revisited in scientific literature repeatedly. Interestingly, if explored carefully this may open a path towards understanding of actual natural history and pathogenesis of age old syndrome, here we mean it remitting seronegative symmetrical synovitis with pitting edema (RS3PE).[1,2,3,4]

Case series:

Authors report a series of 4 cases of RS3PE encountered during treatment with novel anticancer therapy.

Materials and methods:

We reviewed cases diagnosed in oncology department of affiliated medical college and hospital with diagnosis of RS3PE during year 2022. We collected the data regarding co morbidities, presentation, treatment given and outcome (Table 1).

Definitions:

Low dose prednisolone: ≤ 7.5 mg/day.

Medium dose prednisolone: > 7.5 mg/day but ≤ 30 mg/day.

Medium to low dose prednisolone therapy (MLDPT): Induction dose started in medium dose and gradually tapered to low dose for maintenance. Maintenance duration individualized till complete response.

Results and analysis:

In our case series, four patients were diagnosed with RS3PE. Two were males and 2 were females. Three patients had metastatic renal cell carcinoma (RCC) and were on pazopanib treatment. One patient had metastatic head and neck squamous cell carcinoma (HNSCC) and was on treatment with nivolumab. Patient factors noted in table 1 and individual case reports follow.

Table 1: Analysis of cases studied.

	Case 1	Case 2	Case 3	Case 4
Age	47	56	40	70
Sex	F	M	F	M
Cancer	RCC	RCC	RCC	HNSCC
Anticancer therapy	Pazopanib	Pazopanib	Pazopanib	Nivolumab
Joints involved	Bilateral PIP, DIP, MCP, ankle, knee, and unilateral wrist and DRUJ, feet	Bilateral PIP, DIP, knee, ankle, feet	Bilateral PIP, DIP, knee, ankle, feet	Bilateral PIP, DIP, knee, ankle, lower back, feet
ESR	80	86	75	70
CRP	22	24	18	16
RF	Negative	Negative	Negative	Negative
Anti –CCP	Negative	Negative	Negative	Negative
ANA	Negative	Negative	Negative	Negative
Sr. creat (mg/dl)	1.5	1.3	1	1.4
X-ray	Normal	Normal	Normal	Normal
USG	Tenosynovitis	Tenosynovitis	Tenosynovitis	Tenosynovitis
Treatment	Antibiotics, nonnephrotoxic	nonnephrotoxic analgesics (tramadol)	NSAIDs, SSZ and HCQ, MLDPT.	Tramadol /paracetamol, HCQ, MLDPT.

	analgesics, HCQ and MLDPT.	/paracetamol), HCQ and MLDPT.		
Complete Remission of arthritis after steroids.	In 1 month	In 6 weeks	In 3 weeks	In 5 weeks
Impact on anticancer therapy	Pazopanib continued	Pazopanib discontinued till hypertension control	Pazopanib continued	Nivolumab continued
Relapse in median 9 month follow up	No	No	No	No

Case report 1:

Forty seven year female who was a known case of metastatic right side RCC (with liver and pulmonary metastasis) for 10 months on treatment with pazopanib presented with sudden onset pain, tenderness, and swelling and morning stiffness of small joints of both hands and both legs. Her cancer was responding to pazopanib treatment. She had previous history of recurrent renal stones, recurrent urinary tract infection fluctuating serum creatinine (sr. creat) levels (1.5 mg/dl and below). She also gave history of acute gastroenteritis and hospitalization just 2 months back.

She was now prescribed a combination of oral tramadol with paracetamol along with work up for arthritis. She was not having previous rheumatological history.

After 1 week she presented with progression of symptoms and investigations revealed erythrocyte sedimentation rate (ESR) of 80 /hr, C-reactive protein (CRP) 22 mg/dl, rheumatoid factor (RF) negative, Anti-cyclic citrullinated peptide (*anti-CCP*) antibody negative, antinuclear antibody (ANA) negative. Complete blood count (CBC) was normal. Urine showed 40 pus cells/ high power field (HPF), culture was negative. Serum Uric acid level (UA) was normal. X-ray radiography was normal and ultrasound showed tenosynovitis. Magnetic resonance imaging (MRI) of hand showed bilateral changes of synovitis involving proximal interphalangeal joint (PIP) joint, distal interphalangeal joint (DIP) metacarpophalangeal (MP) joint of thumb, the distal radioulnar joint (DRUJ) and wrist surrounding the carpus without any bony erosion. Though involvement of joints was more or less symmetrical, the extent of involvement was not symmetrical.

So the clinical picture consisted of bilateral symmetrical arthritis (pain, tenderness, swelling, redness) of small joints of hands (PIP, DIP, MCP) and bilateral knee and ankles. Grade 3 Pitting edema was noted over legs and feet (figure1). There were no signs of sepsis. Thus the diagnosis of RS3PE was confirmed, reactive arthritis was another possibility.

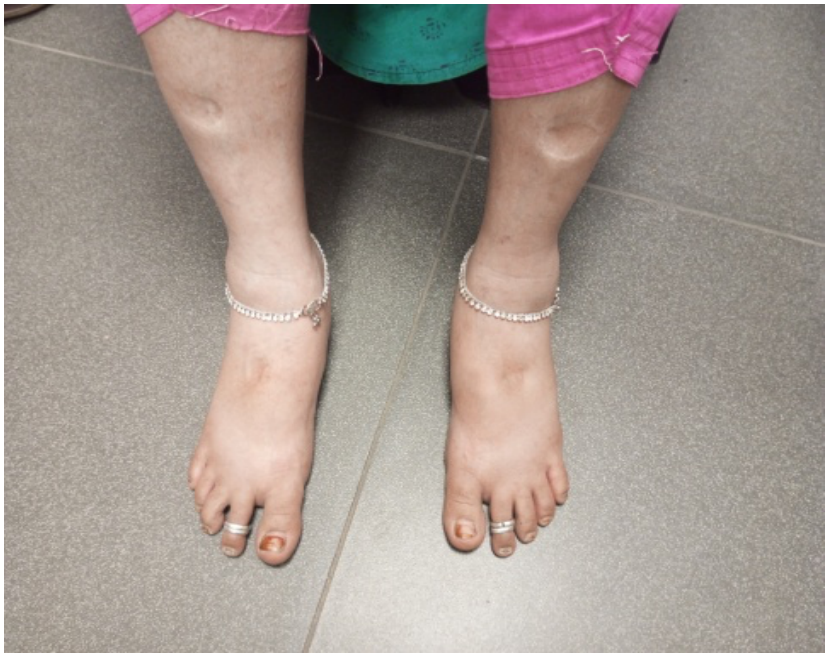

Figure 1: Shows pitting edema with symmetrical synovitis of lower limbs in a female.

Patient was treated with antibiotics, non-nephrotoxic analgesics, hydroxychloroquine (HCQ) and MLDPT (after 2 week no response to other agents).

Case report 2: Fifty six year male, a known case of metastatic RCC on pazopanib for 10 months presented with accelerated hypertension (due to missed regular antihypertensive dose) and pulmonary overload. He also reported bilateral small joint pain, swelling, tenderness and morning stiffness of hands and knee and ankle along with back pain and pitting edema (on examination grade 4) all of which was recent onset (figure 2).

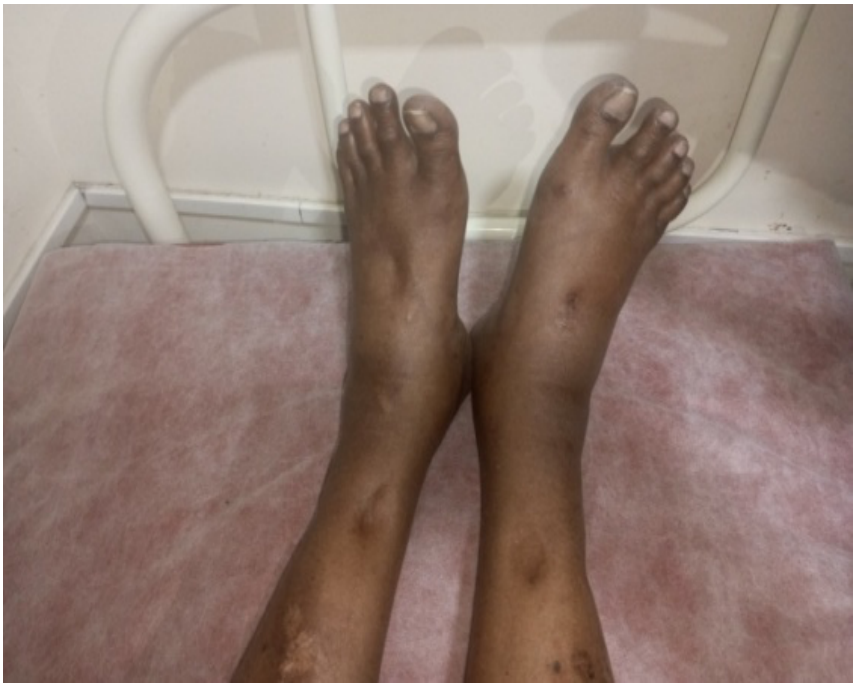

Figure 2: Shows pitting edema with symmetrical synovitis of lower limbs in a male.

Investigations revealed seronegativity (Negative RF and Anti CCP), high ESR (86mm/hr) and high CRP (24 mg/dl). Urine report was normal. CBC and UA were normal. X-ray radiography of joints was normal. Ultrasound of involved joints confirmed tenosynovitis.

Along with appropriate treatment for hypertension, rheumatological diagnosis of RS3PE was established, which was treated with nonnephrotoxic analgesics (tramadol /paracetamol), HCQ with no response. MLDPT therapy was started after 2 weeks to which he responded and pazopanib was discontinued temporarily until hypertension control.

Case report 3:

Forty year female, a known case of metastatic RCC on pazopanib treatment for 9 months presented with mild joint pain, swelling, tenderness and morning stiffness since 2 weeks over small joints of hands and feet. Bilateral ankle, knee, PIP, DIP were involved. ESR (75 mm/hr) and CRP (18 mg/dl) were also elevated. She also demonstrated seronegativity (normal RF and anti-CCP levels). Her sr. creat, UA, CBC and urine reports were normal. On examination grade 3 pitting edema was noted. X-ray radiography was normal. Ultrasound showed features of tenosynovitis in involved joints.

She was treated with non-steroidal anti-inflammatory agents (NSAIDs), sulphasalazine (SSZ) and HCQ. MLDPT was started after 2 weeks for less response to these drugs. She responded dramatically and pazopanib was continued.

Case report 4:

Seventy years male with HNSCC (oropharynx) was treated with cetuximab with radiation. After 3 months, pet CT scan showed residual local disease with a few pulmonary metastases. He was started on 2 weekly nivolumab 240 mg based therapy. After 6 sessions of nivolumab, he developed sudden onset mild bilateral small joint swelling of hands and feet. Later both knees and lower back also showed similar symptoms. Grade 2 pitting edema was noted. ESR (70mm/hr) and CRP (16 mg/dl) were elevated. Sr. creat was 1.4 mg/dl. UA and CBC were normal. X-ray of involved joints did not show erosions, but ultrasound confirmed features of tenosynovitis.

He was initially treated with tramadol /paracetamol, HCQ. Later MLDPT was started after 15 days for less response to joint swelling. Patient responded, and further continued immunotherapy.

Systemic review of literature:

Material and methods:

Figure 3 Flow chart shows systematic literature search and study selection process of the RS3PE in oncology setting with relation to novel drugs. Out of extensive literature (n=3187), we excluded old reports than 2015(n=1593), duplicates (n=796), irrelevant literature (400). From the remaining records (N=396), articles not dedicated to RS3PE (n=270) again excluded. Then for remaining 126 records, we applied inclusion criteria as RS3PE in oncology setting, novel drug treatment, immunotherapy, targeted therapy, available demography. We excluded (N=112) reports in non-oncology setting and reports where details of treatment outcomes were not mentioned. Thus we evaluated 14 records and 2 more were included which had discussion on mechanism of RS3PE occurrence (N=14+2=16). Table 2 shows systematic review of literature of oncorheumatological RS3PE in available data bases.

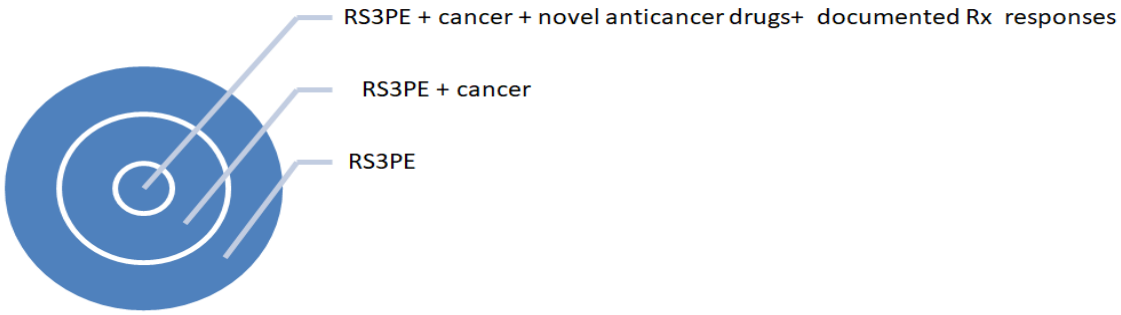

Figure 1: Flow chart showing systematic literature search and study selection process of the RS3PE in oncology setting with relation to novel drugs.

Identification of studies via databases.		
Identification	Result of literature searching (3187), Pubmed (214), pubmed central (221), Scopus (389), Google scholar (2330), DOAJ(33)	Records removed before screening: Older than 2015. (n=1593), Duplicate (n = 796), Other reasons e.g. irrelevance (n=400).
Screening	Suitable records filtered (n=396)	Relevance screening done based on article titles dedicated to RS3PE., More records excluded (n= 270)
	Reports sought for retrieval (n=126)	Reports not retrieved. (n=0)
	Full-text articles assessed for eligibility (n=126)	Inclusion criteria RS3PE in oncology setting, novel drug treatment, immunotherapy, targeted therapy, demography **Exclusion criteria:** non oncology setting, details of treatment outcomes not mentioned, Reports excluded:(n= 112)
Included	Included literatures (n=14) + two articles significant for mechanism of RS3PE added =16.	

Table 2: Summarizes systemic review of reported literature. [1-8]

S.N.	Author	Age in yrs	Sex	Disease	Profile of arthritis.	Special remark other than seronegativity	Drug associated.	Treatment given	Withdrawal of rx
1	Onur bas , Aaral ozbek, Denizcan guven et al	60	M	Renal cell carcinoma	Both hands		Pembrolizumab, pazopanib.	Prednisolone 10 mg/day	N
2.	Aoshima y, Karayama m, Sagisaka s, et al.	69	M	Lung cancer Nsclc	Paraneoplastic bazex syndrome + rs3pe. Pitting edema of the fingers and	High serum VEGF levels.	Pembrolizumab	Not reported	N

					legs, desquamating eruptions on the extensor side of the fingers and ears, and deformities of the distal interphalangeal (dip), proximal interphalangeal, and metacarpophalangeal joints.				
3	Kodama s, kurose k, Mukai t, et al.	48	F	Nsclc	Bilat. shoulder and knee	Elevate matrix metalloproteinase levels	Nivolumab	Low dose prednisolone	N
4	Ngo l, Miller e, Valen p, et al	70	M	Melanoma	Bilat knee, hands, feet		Nivolumab	0.5 mg /kg prednisolone	N
5.	Marie-léa gauci, Barouyr baroudjian, Pauline laly et al	80	M	Melanoma	Hand, wrist, ankle		Nivolumab	0.5 mg/kg prednisolone for 9 months	Y. Stopped for 1 month till CRP normalization.
6.	Tawnie j braaten, Julie r brahmer, Patrick m forde,et al	Mean 58.5 yrs In total 60 patients	32 f, 28 m	Melanoma: 21 (35) nsclc: 14 (23.3) other: 11 (18.3) gastrointestinal: 7 (11.7) genitourinary: 4 (6.7) gynecologic: 3 (5)	Median baseline 28 swollen joint count was 6, and the median baseline 28 tender joint count was 2. Median clinical disease activity index was 17.5,	Pitting edema not commented	Combination therapy (anti-ctla-4+anti-pd-1) was used in 30%. Monotherapy with anti-ctla-4, anti-pd-1 or anti-pdl-1 was used in 70% of patients.	Steroid 20, Cs DMARD 19, BDMARD 11, any DMARD 24, NSAID 7,	Y. Persistent arthritis after 6 months of cessation.
7.	Nikolaos spathas, Panagiota economopoulou, Myrto cheila et al.	55	M	Head and neck	Starts with one knee, spreads to both knees and both hands.	Pitting edema not specified	Pembrolizumab	Prednisolone 5 mg bd, methotrexate 7.5 mg weekly	Y. permanent discontinuation.
8	Chan mm, Kefford rf, Carlino m, et al.	60	M	Melanoma	Both knees, both ankles,	Non pitting edema	Pembrolizumab	Palmindronate Salazopyrin Opioids	Y. Withheld 1 month. Then restarted.
		68	F	Melanoma	One knee, then both knees, then radioulnar, radiocarpal and intercarpal joints	Edema not specified.	Pembrolizumab	NSAID, HCQ, Opioids	Y. 3 month withheld followed by permanent cessation due to persistent symptom

Discussion:

RS3PE is reported in oncological setting but its association with immunotherapy (checkpoint inhibitors and anti CTLA4 agents) and targeted therapy like TKI is underlined with this series. Prompt treatment with MLDPT helped to ameliorate symptoms and provided much needed relief to the patient. To enable this awareness on part of treating oncologist is important. RS3PE, although commonly known among rheumatologists, others may not be aware of this entity and find themselves confused especially with negative rheumatoid factor and arthritis directed investigations. There are some

individual reports but most of them fail to provide guidance on management. We are publishing first such series to our knowledge and we have also attempted systematic review for treating such patients. Various cancer like colon, stomach, prostate, lung, lymphoma, malignant melanoma, head and neck cancer and their treatments have been also reported with this condition. So cancer associated inflammatory microenvironment can also be causation. Table 2 summarizes systemic review of literature. [1-8]

Many cases of RS3PE are documented in elderly population. That might be just because underlying co morbidities and therapeutic agents are prevalent currently in same setting. As more cases are being reported, age looks to involve middle age and young age also. Youngest case reported is 20 years female. So age should not be a criterion for diagnosis. This is important because all the oncological medicines get their approvals in metastatic diseases in adults followed by adjuvant and neoadjuvant setting and later they are extrapolated in pediatrics also, once safety and efficacy is established. [9]

It has been generally reported in elderly males but on case reports we cannot derive sex predilection. But it's clear that it's a non female preponderant disease (against other autoimmune diseases). In our case series out of 4 cases, 2 were males and 2 were female.

As it's a seronegative inflammatory arthritis, it has some overlap to reactive arthritis. While reactive arthritis is generally peripheral, asymmetric, additive and oligoarticular, RS3PE is symmetrical by definition itself. But as we see carefully, the reported literature presentations and radiological pictures in all cases are not strictly symmetrical, at least to start with. As the disease is rapidly evolving, there can be phases of asymmetry and symmetry. Again, if treated early signs of symmetry can be easily missed. Also in long standing chronic inflammatory disease like cancer, reactive arthritis can take an atypical symmetrical course (due to recurrent and chronic inflammatory insults). So one can consider as RS3PE is symmetrical disease phase, can be asymmetrical initial to start with. Also, pitting edema is not specified in many case reports of inflammatory symmetrical arthritis. But at the stage of pitting edema, disease reported is generally symmetrical. [1-8]

For satisfying the word "remitting", one has to wait till disease remission. So it can be only a retrospective diagnosis. If treated improperly, erosive disease may develop and disease may have a propensity to last for long time even 6 to 9 months and even thereafter leading to compelled removal of inciting therapeutic anticancer agent as well as diagnostic dilemma. There lies importance of early addition of steroids which has diagnostic as well as therapeutic significance. [1-8, 10]

Generally steroids are not added until completion of basic workup. But if not treated early with steroids, then progression of pitting edema is unavoidable as a part of complication. Pitting edema is more common in patients with underlying renal, liver diseases, chronic protein deficiency with superimposed local abnormality. It is just a sign of fluid accumulation. If untreated even at stage of pitting edema, patient can land up in pulmonary edema due to decompensated underlying disease. [10, 11]

In general typical reactive arthritis is self limiting condition but RS3PE needs aggressive intervention. Steroids may be required to manage emergency crisis as well as to alter overactive immune response secondary to novel anticancer therapies. Onset of action of steroids is much faster than other disease modifying antirheumatic drugs (DMARDs), which may have role in long term management as steroid sparing agent. [10, 11]

Also patients should be monitored for proteinuria, as both these group of

pharmacological agents (check point inhibitors and tyrosine kinase inhibitors acting on VEGF) have propensity for nephrotoxicity. Steroid response to pitting edema can be secondary to steroid response to nephrotoxicity of these agents. [12.13]

Chronic kidney disease (CKD) including RCC is chronic state of inflammation and prone for recurrent urinary tract infections, hematuria and hence reactive inflammatory arthritis should not surprise. Typical reactive arthritis follows urinary or gastrointestinal infection which is asymmetrical and self-remitting but reactive inflammatory arthritis which follows chronic underlying inflammatory condition can take atypical symmetrical form, last longer than usual, and requires aggressive treatment to prevent complications. [12, 13]

CKD, RCC as well as RS3PE all are known to have association with increased serum levels of VEGF. Pazopanib being an anti-VEGF agent act by decreasing VEGF (also acts on PDGF, FGF, and C-KIT). So in initial few months there is good response to RCC. Later as a resistance mechanism develops, there may be gradual increase in VEGF on treatment with pazopanib, which may manifest as inflammatory seronegative arthritis. Addition of some other anti-VEGF agents for treatment of arthritis may help theoretically even if pazopanib is continued. [14]

For sudden or recent onset arthritis, though joint radiography can be done as baseline investigation, but it takes more than 3 months for erosions to appear on x-ray. Practically it has no role in diagnosis. [12-16]

Musculoskeletal ultrasound can show early signs of synovitis but it's not available easily and it requires expertise to interpret. [12-15]

Considering the seriousness of condition, treatment delay is not advised. Early initiation of anti-inflammatory agents, DMARDs and especially steroids can decrease the morbidity. [10]

Since it is a remitting disease, no long term steroid is required in most of the cases. And steroid doses can be reduced on maintenance to less than or equal to 10 mg/day. Literature suggests some patients required more than 6 -9 months treatment and permanent withdrawal of ongoing immunotherapy or targeted therapy. That can be due to delay in diagnosis and addition of steroids after establishment of erosive disease. Early addition of steroids has made most of patients to continue on same therapeutic agent for longer time. [10]

When due to renal dysfunction, it's not feasible to add NSAIDs for arthritis treatment; steroids become essential to control inflammation because nonnephrotoxic analgesics like tramadol, paracetamol have very minimal anti-inflammatory activity. [10]

Cancer associated inflammatory microenvironment; increased VEGF levels, matrix metalloproteinase levels, IL-6 and TNF alpha are also linked in causative mechanism of RS3PE. [12-16]

We can categorize this seronegative inflammatory synovitis as table no 3.

Table 3: We can categorize this seronegative inflammatory synovitis as table no 3.

Grade 1	Asymmetrical joint involvement/ synovitis without pitting edema
Grade 2	Symmetrical polyarticular joint involvement/ synovitis without pitting edema
Grade 3	Symmetrical joint involvement/ synovitis with pitting edema (RS3PE)
Grade 4	Florid edema, pulmonary edema, ascitis. (This is generally unrelated to joint involvement severity but related to underlying medical co morbidity).

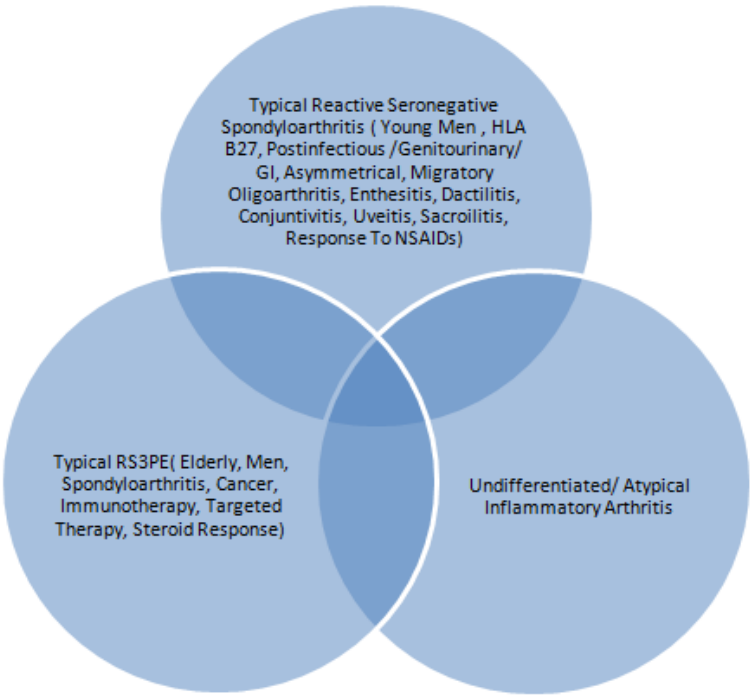

Figure 4: describes common overlapping picture of typical reactive arthritis, typical RSE3PE and undifferentiated or atypical inflammatory arthritis.

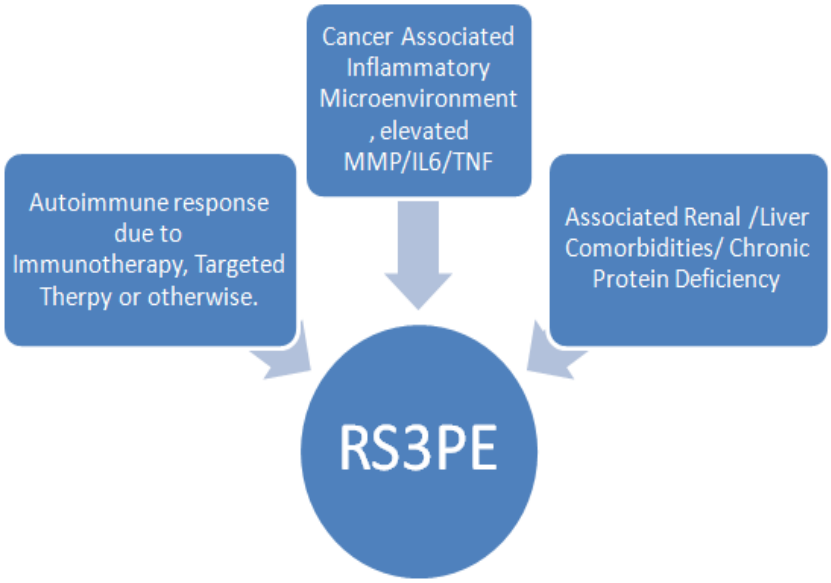

Figure 5: describes predisposition and mechanism of occurrence of RS3PE.

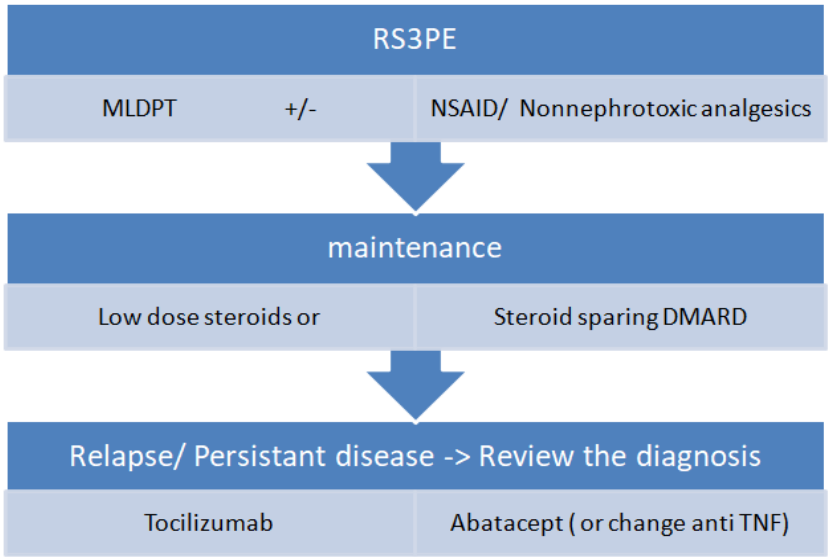

Figure 6: describes treatment algorithm of treatment of RS3PE.

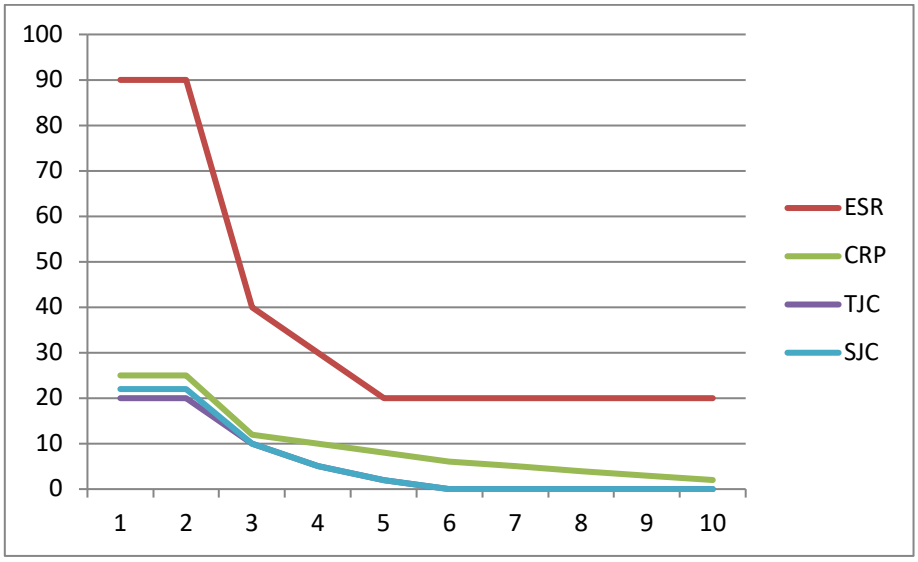

Figure 7: Shows dramatic improvement with MLDPT in disease activity after 2nd week in our patients represented by ESR, CRP, TJC (tender joint count) and SJC (swollen joint count) values in graph.

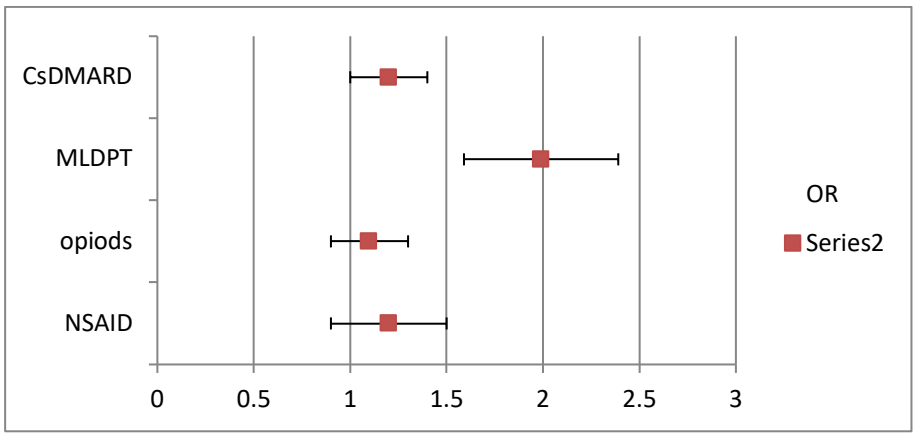

Figure 8 summarizes forest plot representation of various studies stating efficacy of individual drugs, finally favoring MLDPT and other drugs inconclusive.

Limitations:

This is not a case control or randomized study. Also, there are no randomized case control studies available in literature. 'Dramatic response' consistently reported in literature is taken as significant and 'no response' consistently reported in literature taken as insignificant.

Conclusion:

RS3PE is a common interesting clinical picture in oncorheumatological setting and both oncologist and rheumatologist should be aware of associations (cancer, targeted and immunotherapy), natural history (fluid retention and its complications), intervention (MLDPT) and outcomes (continuation or interruption of inciting pharmacological agents).

Funding information:

The study was not funded by any agency.

Ethical approval:

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments.

Informed consent:

There is no disclosure of patient's personal identity and informed consents were obtained. It's purely observational, non-interventional study.

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