bFGF could be a Biomarker of Malignancy in RS3PE Syndrome: an Ambispective Single Center Cohort Analysis of 51 Patients

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Abstract

Objectives

Remitting seronegative symmetrical synovitis with pitting edema (RS₃PE) is a rare inflammatory arthritis, with a higher incidence of malignancy. The aim of this study is to identify biomarkers for predicting malignancy in RS₃PE.

Methods

A total of 51 patients with RS₃PE from September 2007 to May 2019 were retrospectively reviewed and followed for up to 5 years, with 15 patients with osteoarthritis (OA) and 14 patients with elderly-onset rheumatoid arthritis (EORA) as disease controls. Serum levels of angiogenesis cytokines were measured by electrochemiluminescent immunoassay and Luminex Human Magnetic Assay. Clinical data and laboratory parameters were analyzed to identify risk factors for malignancy.

Results

A total of forty-eight RS₃PE patients (94.1%) were available with follow-up data, 8 patients (16.7%) were diagnosed with malignancy, of which 6 patients were hematological tumor, and 2 patients were solid tumor. Serum levels of basic fibroblast growth factor (bFGF) were exclusively higher in RS₃PE patients with malignancy [14.21 (7.52, 23.18) ng/mL] than RS₃PE patients without malignancy [4.32 (2.88, 7.42) ng/mL], OA [3.20 (2.20, 5.30) ng/mL] and EORA [3.20 (2.20, 5.30) ng/mL]. The optimal cut-off value of bFGF for malignancy was 10ng/mL in RS₃PE. Logistic regression analysis indicated that elevation of bFGF was a risk factor for malignancy in RS₃PE.

Conclusions

This study indicated that bFGF was elevated in RS₃PE patients with malignancy and could serve as a biomarker for predicting paraneoplastic RS₃PE.

Introduction

Remitting seronegative symmetrical synovitis with pitting edema (RS₃PE) is a rare elderly-onset inflammatory arthritis, characterized by symmetrical involvement of small joints and marked pitting edema on the dorsum of the hands and feet[1, 2]. In addition, higher incidence of malignancy was reported in RS₃PE after the first symptoms onset or during follow-up[2-4]. However, no significant demographic or clinical differences were observed between idiopathic and paraneoplastic cases of RS₃PE, which suggests the importance of investigating novel serum tumor markers.

Previous studies have found two angiogenesis cytokines, namely vascular endothelial growth factor (VEGF) and matrix metalloproteinase (MMP) -3, were involved in the pathogenesis of RS₃PE along with malignance[5-8]. But later findings indicated that elevated levels of VEGF were also characteristics of infections and organizing pneumonia in RS₃PE[9, 10]. MMP-3 was elevated in RS₃PE patients with solid malignancy[11], but it was also an indicator for active arthritis[12]. It still remains elusive whether there is a specific biomarker for identifying arthritis with malignancy.

Since angiogenesis plays an important role in the pathogenesis and progression of cancer, we simultaneously evaluated the serum levels of 12 angiogenesis cytokines in paraneoplastic RS₃PE, comparing with idiopathic RS₃PE, osteoarthritis (OA) and elderly-onset rheumatoid arthritis (EORA) in the current study. We aimed to discover some novel markers for predicting malignancy in RS₃PE.
Methods

Patients enrolled. A single center cohort study was performed in the department of Rheumatology, Peking University People's Hospital. Fifty-one patients diagnosed with RS$_3$PE syndrome were consecutively enrolled from September 2007 to May 2019, fulfilling the following criteria: (1) bilateral pitting edema of dorsum of hands and/or feet, (2) abrupt onset of polyarthritis, (3) age > 50 years, (4) seronegative for rheumatoid factor (RF)$^{13}$. As disease controls, 15 patients with OA and 14 patients with EORA were also enrolled, with sex and age matched. All the participants in disease control groups were excluded malignancy.

Study design and data collection. Patients with RS$_3$PE were followed up for 5 years, or monitored up to 29$^{th}$ February 2021 if they enrolled after 28$^{th}$ February 2016. The primary clinical outcome was occurrence of malignancy. The baseline clinical and laboratory characteristics, coexistence of malignancy and response to treatment were obtained from the medical records. If no follow-up data was available in our center, we contacted the family members to acquire the physical status (especially the occurrence of malignancy) confirmed by regular medical examination reports.

Measurement of angiogenesis cytokines. The serum samples were collected from 45 RS$_3$PE patients and all diseases controls at baseline and stored at-80°C in polypropylene microfuge tubes without thawing before test. Serum levels of VEGF-A, VEGF-C, VEGF-D, FMS-like tyrosine kinase 1 (Flt-1), Tie-2, placental growth factor (PIGF) and basic fibroblast growth factor (bFGF) were measured via electrochemiluminescent immunoassay by V-PLEX Plus Angiogenesis Panel 1 Human Kit (Meso Scale Discovery). Serum levels of MMP-1, MMP-3, MMP-7, mesothelin and tumor necrosis factor related apoptosis inducing ligand (TRAIL) were determined with Luminex Human Magnetic Assay (5-Plex) LXSAHM-05 (R&D).

Statistical analysis. Data analyses were performed using SPSS 23.0 for Windows. Continuous data with normal distribution were expressed as the mean ± standard and differences between groups were analyzed by one-way ANOVA. Continuous data with skewed distribution were expressed as median (P25, P75) and differences between groups were analyzed by Kruskal-Wallis test. Dichotomous variables were reported as frequency (percentages) and differences between groups were compared using the chi-square test (or Fisher exact test when appropriate). The cut-off value of bFGF in RS$_3$PE patients with malignancy was determined by Receiver Operating Characteristic (ROC) methods. Univariate and multivariate logistic regression analysis were adopted to identify risk factors of malignancy. The variables assessed in univariate regression analysis were entered as independent variables in multivariate logistic regression analysis when P value <0.1. Two-sided P < 0.05 was considered statistically significant. P value was adjusted by Bonferroni correction in multiple tests.

Results

Clinical and laboratory features of RS$_3$PE patients

The clinical and laboratory features of overall RS$_3$PE patients were shown in Table 1. Forty-eight patients (94.1%) were available with follow-up data, and a total of 26 patients (54.1%) completed a 5-year follow-up, and the follow-up time for the remaining 22 patients ranged from 1 month to 54 months. During the study period, eight of them (16.7%) were diagnosed with malignant tumors. Twenty-eight patients (54%) were male and the average age at onset was 73.24±9.23 years. Pitting edema was seen in the hands of 45 patients (88.2%) and in the feet of 27 patients (88.9%). Weight loss was seen in 19 patients (37.3%). Patients had an elevated level of C reactive protein (CRP) (43.9 [22.8, 82.0] mg/dL) and erythrocyte sedimentation rate (ESR) (55.37±34.12 mm/h). All patients had a normal level of carcinoembryonic antigen (<4.7 ng/mL). Eight patients (17.4%) had an elevated level of neuroenolase (>16.3ng/mL), 3 patients (5.8%) had an elevated level of cytokeratin 19 fragment (>3.3ng/mL), 2 patients (3.9%) had an elevated level of carbohydrate antigen.
19-9 (>39U/mL), and only one patient (1.9%) had an elevated level of alpha fetoprotein (>7ng/mL). Antinuclear antibody (ANA) was positive (≥1:80) in 6/51 (11.8%), and anti-Ro-52 was positive in 5/51 (9.8%). The median of initial prednisolone dose was 15 mg/day, and 44/51 (89.8%) showed good response to prednisolone.

**Comparison between RS<sub>3</sub>PE patients with and without malignancy**

The detailed clinical profiles of the eight RS<sub>3</sub>PE patients with malignancy were displayed in Table 2. The prevalence of malignancy was 16.7% (8/48); six were hematological tumors, and 2 were solid tumors. The time from the onset of arthritis to confirmation of malignancy was from 2 months to 3 years. In these 6 patients with hematological tumors, 4 patients were diagnosed within 6 months from arthritis onset, and 3 patients showed poor response to low-dose prednisolone. Both of the two patients with solid tumors were diagnosed 2 years after arthritis onset, and one of them (50%) was resistant to low-dose prednisolone.

We next compared the clinical and laboratory features between patients with or without malignancy (Table 1). Better response to prednisolone was found in patients without malignancy (n=38/40, 97.4%) than patients with malignancy (n=3/7, 42.8%). However, significant differences were not seen in demographic figures (age and gender), clinical features (patterns of edema and weight loss) and laboratory features (CRP, ESR, immunoglobulin, complement and tumor markers).

**Serum levels of angiogenesis cytokines among RS<sub>3</sub>PE with/without malignancy, OA and EORA**

Twelve angiogenesis cytokines were measured and the results were demonstrated in Table 3. Serum levels of bFGF were exclusively higher in RS<sub>3</sub>PE patients with malignancy [14.21 (7.52, 23.18) ng/mL] than RS<sub>3</sub>PE patients without malignancy [4.32 (2.88, 7.42) ng/mL], OA [3.23 (1.96, 5.59) ng/mL] and EORA [3.20 (2.20, 5.30) ng/mL]. However, there were no significant differences in serum levels of VEGF-A, VEGF-C, VEGF-D, Flt-1, Tie-2, PIGF, MMP-1, MMP-3, MMP-7, mesothelin and TRAIL among different groups. Figure 1 showed the ROC curve of bFGF with an AUC value of 0.817, and the optimal cut-off value was 10ng/mL; the sensitivity was 75% and the specificity was 89.5%.

**Risk factors for malignancy in RS<sub>3</sub>PE**

As shown in table 4, the results of univariate logistics models found that bilateral pitting edema of hands (OR=0.074, 95%CI (0.006 - 0.968), P=0.047) and good response to prednisolone (OR=0.039, 95%CI (0.005 - 0.311), P=0.002) were negatively associated with malignancy in RS<sub>3</sub>PE, and elevation of bFGF (>10ng/mL) (OR=14.084, 95%CI (2.421 - 83.332), P=0.003) was positively associated with malignancy in RS<sub>3</sub>PE. Then the multivariate logistic models showed elevation of bFGF was a unique risk factor for malignancy (OR=14.667, 95%CI (2.029 - 106.038), P=0.008).

**Discussion**

In the present study, we reviewed the clinical and laboratory features and simultaneously analyzed multiple angiogenesis cytokines in RS<sub>3</sub>PE patients with malignancy. We found elevation of bFGF might be a useful predictor for malignancy in RS<sub>3</sub>PE.

Increased associated malignancy in RS<sub>3</sub>PE has been reported since 1985, including hematological malignancies and solid tumors<sup>[2, 14-16]</sup>, and the average malignancy rate was estimated to 20%<sup>[2]</sup>, which is similar to our study. Although hematological malignancies were the primary tumors in our study and most of them were diagnosed within the first 6 months, both of the two associated solid tumors were confirmed during the follow-up. Besides, a French study of six men with RS<sub>3</sub>PE demonstrated that all solid malignancy was discovered during a five-year follow-up<sup>[17]</sup>. These findings
indicate that solid tumor might be relatively insidious in RS₃PE related malignancies, reminding rheumatologists the importance of tumor screening during the follow-up.

Poor response to low-dose prednisolone is associated with malignancies in RS₃PE in our study, and some reported cases of paraneoplastic RS₃PE are also revealed poor response to glucocorticoid. However, rapid response to glucocorticoid therapy is also found for some paraneoplastic RS₃PE, and there are no clinical variables for predicting malignancy in RS₃PE[1, 3, 4, 19], which calls for more effective biomarkers.

Interestingly, our study discovered bFGF is the only angiogenesis cytokine which is elevated particularly in RS₃PE associated malignancy, and further multiple logistic regressions revealed elevation of bFGF may serve as a marker for predicting malignancy in RS₃PE. bFGF, also known as fibroblast growth factor 2 (FGF-2), is one of the prototypes of the FGF family, which signals through FGF receptors (FGFRs) and promotes growth and differentiation of a broad spectrum of cell types, including dermal fibroblasts, keratinocytes, endothelial cells and melanocytes[20-22]. In addition, bFGF also plays critical role in promoting tumor angiogenesis and metastasis, and has been shown to be involved in the invasion and progression of solid and hematological malignancies[21, 23-26].

Apart from tumor genesis, it has also been found that bFGF could stimulate osteoclastogenesis and promote bone absorption through binding to FGFRs, and is the only one of the bone-resorptive cytokines that is highly expressed in the synovial fluid of RA patients[27-29]. Thus, significantly higher serum bFGF in RS₃PE may reflect the secretion of bFGF in situ of tumor tissues as well as synovium, suggesting that bFGF might play an important role in the pathogenesis of RS₃PE. Besides, the titers of bFGF were relatively lower in the RS₃PE associated solid malignancy (confirmed after 2 years from arthritis onset) than RS₃PE associated hematological malignancy (confirmed within 1 years from arthritis onset), which might partially due to the late onset of solid tumor.

Previous researches have pointed out that RS₃PE might be a VEGF associated disorder and elevated serum level of VEGF was also found in paraneoplastic RS₃PE[6, 7]. However, recent study has found serum VEGF is elevated in many elderly patients with different rheumatic diseases, indicating that VEGF may not be a marker for predicting malignancy[30]. Tomoki O. et al reported high serum MMP-3 is characteristic of RS₃PE patients with neoplasm. Nevertheless, serum levels of MMP-3 are relatively lower in our paraneoplastic RS₃PE patients compared with non-paraneoplastic RS₃PE patients. This difference might be partially due to different kinds of malignancy. All of the cancers in Tomoki O. et al’s study are solid tumors and they merely compared the difference of serum MMP-3 between patients with and without malignancy[11]. Most of our paraneoplastic RS₃PE patients are hematological, and we utilized multiple logistic models to fully confirm the relationship between bFGF and malignancy.

Limitations

Due to the rarity of RS₃PE, the number of associated malignant cases is relatively less at single center, therefore, a prospective cohort or multi-center studies are needed to confirm the clinical significance of bFGF in further studies.

Conclusion

Our study revealed the clinical significance of serum bFGF in RS₃PE, thus bFGF is a predictor for malignancy in RS₃PE. Further researches might verify our findings by multi-center studies and explore the prognostic value for angiogenesis cytokines.

Abbreviations
Declarations

Ethical Approval and Consent to participate

The study was approved by the ethics committee of Peking University People's Hospital (2020PHB060) and the study complied with the Declaration of Helsinki guidelines. All the participants were given written information consent.

Consent for publication

Not applicable

Availability of supporting data

Dr. Hua Ye and Dr. Yuzhou Gan had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis

Competing interests

All authors declare that they have no competing interests.

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Authors' contributions

YZG: data interpretation and analysis, manuscript drafting, review and editing. HY: methodology, review and editing. JLC, YCZ and XL: clinical data collecting and follow-up of participants. YS and YFW: laboratory analysis. The authors read and approved the final manuscript.

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References

[1] Manger B, Schett G. Paraneoplastic syndromes in rheumatology. Nat Rev Rheumatol. 2014. 10(11): 662-70.
[2] Li H, Altman RD, Yao Q. RS3PE: Clinical and Research Development. Curr Rheumatol Rep. 2015. 17(8): 49.
[3] Karmacharya P, Donato AA, Aryal MR, et al. RS3PE revisited: a systematic review and meta-analysis of 331 cases. Clin Exp Rheumatol. 2016. 34(3): 404-15.
[4] Russell EB. Remitting seronegative symmetrical synovitis with pitting edema syndrome: followup for neoplasia. J Rheumatol. 2005. 32(9): 1760-1.
[5] Kenzaka T. The Relationship between Remitting Seronegative Symmetrical Synovitis with Pitting Edema and Vascular Endothelial Growth Factor and Matrix Metalloproteinase 3. Intern Med. 2020. 59(8): 1021-1022.
[6] Tabeya T, Sugaya T, Suzuki C, et al. A case of angioimmunoblastic T-cell lymphoma with high serum VEGF preceded by RS3PE syndrome. Mod Rheumatol. 2016. 26(2): 281-5.
[7] Arima K, Origuchi T, Tamai M, et al. RS3PE syndrome presenting as vascular endothelial growth factor associated disorder. Ann Rheum Dis. 2005. 64(11): 1653-5.
[8] Kenzaka T, Goda K. Serum matrix metalloproteinase 3 in detecting remitting seronegative symmetrical synovitis with pitting edema syndrome: A case report. World J Clin Cases. 2018. 6(5): 84-87.
[9] Hosoda C, Ishiguro T, Morimoto Y, et al. Remitting Seronegative Symmetrical Synovitis with Pitting Edema Syndrome Complicated with Organizing Pneumonia. Intern Med. 2020. 59(8): 1065-1069.
[10] Drago F, Ciccarese G, Agnoletti AF, et al. Remitting seronegative symmetrical synovitis with pitting edema associated with parvovirus B19 infection: two new cases and review of the comorbidities. Int J Dermatol. 2015. 54(10): e389-93.
[11] Origuchi T, Arima K, Kawashiri SY, et al. High serum matrix metalloproteinase 3 is characteristic of patients with paraneoplastic remitting seronegative symmetrical synovitis with pitting edema syndrome. Mod Rheumatol. 2012. 22(4): 584-8.
[12] Tuncer T, Kaya A, Gulkesen A, Kal GA, Kaman D, Akgol G. Matrix metalloproteinase-3 levels in relation to disease activity and radiological progression in rheumatoid arthritis. Adv Clin Exp Med. 2019. 28(5): 665-670.
[13] Olivé A, del Blanco J, Pons M, Vaquero M, Tena X. The clinical spectrum of remitting seronegative symmetrical synovitis with pitting edema. The Catalán Group for the Study of RS3PE. J Rheumatol. 1997. 24(2): 333-6.

[14] Gisserot O, Crémades S, Landais C, Leyral G, Bernard P, de Jauréguiberry JP. RS3PE revealing recurrent non-Hodgkin's lymphoma. Joint Bone Spine. 2004. 71(5): 424-6.

[15] Tunc SE, Arslan C, Ayvacioglu NB, Sahin M, Akkus S, Yorgancigil H. Paraneoplastic remitting seronegative symmetrical synovitis with pitting edema (RS3PE syndrome): a report of two cases and review of the literature. Rheumatol Int. 2004. 24(4): 234-7.

[16] Chiappetta N, Gruber B. Remitting seronegative symmetrical synovitis with pitting edema associated with acute myeloid leukemia. J Rheumatol. 2005. 32(8): 1613-4.

[17] Sibilia J, Friess S, Schaeverbeke T, et al. Remitting seronegative symmetrical synovitis with pitting edema (RS3PE): a form of paraneoplastic polyarthritis. J Rheumatol. 1999. 26(1): 115-20.

[18] Paira S, Graf C, Roverano S, Rossini J. Remitting seronegative symmetrical synovitis with pitting oedema: a study of 12 cases. Clin Rheumatol. 2002. 21(2): 146-9.

[19] Lakhmalla M, Dahiya DS, Kichloo A, Fatima T, Edigin E, Wani F. Remitting seronegative symmetrical synovitis with pitting edema: a review. J Investig Med. 2021. 69(1): 86-90.

[20] Pallotta MT, Nickel W. FGF2 and IL-1β - explorers of unconventional secretory pathways at a glance. J Cell Sci. 2020. 133(21).

[21] Labanca E, Vazquez ES, Corn PG, et al. Fibroblast growth factors signaling in bone metastasis. Endocr Relat Cancer. 2020. 27(7): R255-R265.

[22] Belov AA, Mohammadi M. Molecular mechanisms of fibroblast growth factor signaling in physiology and pathology. Cold Spring Harb Perspect Biol. 2013. 5(6).

[23] Song MZ, Mao YM, Wu J, Pan HF, Ye QL. Increased circulating basic fibroblast growth factor levels in acute myeloid leukemia: a meta-analysis. Hematology. 2020. 25(1): 186-193.

[24] Ribatti D, Vacca A, Rusnati M, Presta M. The discovery of basic fibroblast growth factor/fibroblast growth factor-2 and its role in haematological malignancies. Cytokine Growth Factor Rev. 2007. 18(3-4): 327-34.

[25] Akl MR, Nagpal R, Ayoub NM, et al. Molecular and clinical significance of fibroblast growth factor 2 (FGF2 /bFGF) in malignancies of solid and hematological cancers for personalized therapies. Oncotarget. 2016. 7(28): 44735-44762.

[26] Chua V, Orloff M, Teh JL, et al. Stromal fibroblast growth factor 2 reduces the efficacy of bromodomain inhibitors in uveal melanoma. EMBO Mol Med. 2019. 11(2).

[27] Nakano K, Okada Y, Saito K, Tanaka Y. Induction of RANKL expression and osteoclast maturation by the binding of fibroblast growth factor 2 to heparan sulfate proteoglycan on rheumatoid synovial fibroblasts. Arthritis Rheum. 2004. 50(8): 2450-8.

[28] Yan D, Chen D, Cool SM, et al. Fibroblast growth factor receptor 1 is principally responsible for fibroblast growth factor 2-induced catabolic activities in human articular chondrocytes. Arthritis Res Ther. 2011. 13(4): R130.
Zhao S, Wang Y, Hou L, Wang Y, Xu N, Zhang N. Pentraxin 3 inhibits fibroblast growth factor 2 induced osteoclastogenesis in rheumatoid arthritis. Biomed Pharmacother. 2020. 131: 110628.

Smets P, Devauchelle-Pensec V, Rouzaire PO, Pereira B, Andre M, Soubrier M. Vascular endothelial growth factor levels and rheumatic diseases of the elderly. Arthritis Res Ther. 2016. 18(1): 283.

Tables

Table 1. Characteristics of RS3PE patients with or without malignancy
|                          | Overall (n=51) | RS<sub>3</sub>PE with malignancy (n=8) | RS<sub>3</sub>PE without malignancy (n=40) | P   |
|--------------------------|---------------|----------------------------------------|-------------------------------------------|-----|
| Age (years)              | 73.39±9.18    | 75.00±11.07                            | 73.50±8.51                                | 0.667|
| Age of onset (years)     | 73.24±9.23    | 74.5±11.30                             | 73.4±8.53                                 | 0.754|
| Gender (M/F)             | 28/23         | 5/3                                    | 21/19                                     | 0.710|
| Pitting edema of hands (n, %) | 45 (88.2)    | 7 (87.5)                               | 35 (87.5)                                 | 1    |
| Bilateral (n, %)         | 42 (93.3)     | 5 (71.4)                               | 34 (97.1)                                 | 0.067|
| Weight loss (n, %)       | 18 (35.3)     | 5 (62.5)                               | 12 (30)                                   | 0.112|
| CEA > 4.7 ng/mL          | 0            | /                                      | /                                         |     |
| AFP > 7ng/mL             | 1 (2.6)‡      | 1 (14.3)§                              | 0※                                        | 0.152|
| CA19-9 > 39U/mL          | 2 (5.1)‡      | 0§                                     | 2 (5.1)※                                   | 1    |
| CYFRA21-1 >3.3 ng/mL     | 3 (6.5)‡      | 1 (14.3)§                              | 2 (5.1)※                                   | 0.398|
| NSE >16.3 ng/mL          | 8 (17.4)‡     | 2 (28.6)§                              | 6 (18.2)※                                 | 0.587|
| C reactive protein (mg/L)| 43.9 (22.8, 82.0) | 35.9 (12.0, 91.0)       | 45.7 (26.4, 84.9)                         | 0.674|
| Erythrocyte sedimentation rate (mm/h) | 55.37±34.12 | 48.88±29.00                           | 56.85±35.81                               | 0.558|
| Immunoglobulin A (g/L)   | 3.05 (1.62, 3.73) | 2.71 (1.18, 3.66)       | 3.13 (1.62, 4.04)                        | 0.734|
| Immunoglobulin G (g/L)   | 12.42±4.74    | 12.56±5.24                            | 12.32±4.81                                | 0.900|
| Immunoglobulin M (g/L)   | 0.71 (0.50, 1.09) | 0.68 (0.50, 1.39)       | 0.71 (0.47, 1.12)                        | 0.968|
| Complement 3 (g/L)       | 1.04 (0.87, 1.28) | 1.03 (0.79, 1.16)       | 1.05 (0.88, 1.29)                        | 0.422|
| Complement 4 (g/L)       | 0.23±0.09     | 0.25±0.04                             | 0.24±0/09                                 | 0.722|
| ANA≥1:80 (n, %)          | 6 (11.8)      | 0                                      | 6 (15)                                    | 0.571|
| Anti-Ro-52 (n, %)        | 5 (9.8)       | 1 (12.5)                               | 4 (10)                                    | 1    |
| Initial prednisolone dose | 15 (15, 30)   | 15 (10, 30)                           | 15 (15, 27.5)                             | 0.946|
| Fast response to prednisolone (n, %) | 44 (89.8)     | 3 (42.8)▲                              | 38 (97.4)                                 | 0.001*|

Note: RS<sub>3</sub>PE: Remitting seronegative symmetrical synovitis with pitting edema. ANA: anti-nuclear antibody. CEA: Carcinoembryonic antigen. AFP: Alpha fetoprotein. CA19-9: Carbohydrate antigen 19-9. CYFRA21-1: Cytokeratin 19 fragment. NSE: Neuroenolase.

Values displayed as n (%), mean ±standard deviation, or median (P25, P75) according to their features of distribution.

†: Five patients did not have the data of serum tumor markers.
※: Two patients did not have the data of serum tumor markers.
§: One patient did not have the data of serum tumor markers.
▲: One patient did not receive glucocorticoids.
*: P<0.05, significant difference between RS₃PE patients with and without malignancy.

Table 2. Detailed clinical profiles of RS₃PE patients with malignancy

| No. | Age/sex | Type of malignancy            | Time from arthritis onset to malignancy confirmation | Signs   | ESR (mm/h) | CRP (mg/L) | bFGF (ng/mL) | Initial pred. (mg/day) | Response to pred. |
|-----|---------|------------------------------|------------------------------------------------------|---------|------------|------------|--------------|------------------------|------------------|
| 1   | 85/M    | Acute myeloid leukemia - M2  | 6 months                                             | unilateral hands | 29         | 16.9       | 25.04        | 0                      | /                |
| 2   | 75/F    | Multiple Myeloma (IgA, λ)    | 2 years                                              | bilateral hands | 61.2       | 70         | 24.35        | 15                     | poor             |
| 3   | 80/M    | Diffuse large B cell lymphoma | 2 months                                             | bilateral hands | 86         | 45.9       | 10.2         | 40                     | poor             |
| 4   | 53/M    | Plasma cell leukemia         | 8 months                                             | unilateral hands | 19         | 177.3      | 42.48        | 30                     | poor             |
| 5   | 85/F    | Rectal Carcinoma             | 3 years                                              | no hands        | 44         | 10.4       | 17.58        | 30                     | poor             |
| 6   | 66/F    | Multiple Myeloma             | 3 months                                             | bilateral hands | 71         | 26.11      | 10.94        | 15                     | good             |
| 7   | 83/M    | non-Hodgkin lymphoma         | 2 months                                             | bilateral hands | 67         | 101        | 5.57         | 15                     | good             |
| 8   | 73/M    | Lung carcinoma               | 2 years                                              | bilateral hands | 5          | 9.39       | 6.63         | 7.5                    | good             |

RS₃PE: Remitting seronegative symmetrical synovitis with pitting edema. CRP: C reactive protein. ESR: erythrocyte sedimentation rate. Pred.: prednisolone.

Table 3. Comparison of angiogenesis cytokines among RS₃PE with/without malignancy, OA and EORA
RS\textsubscript{3}PE with malignancy (n=8) & RS\textsubscript{3}PE without malignancy (n=38) & OA (n=15) & EORA (n=14) & F/t & P \\
Flt-1 (ng/mL) & 7.38±2.64 & 6.14±2.25 & 5.96±1.53 & 5.59±1.67 & 1.321 & 0.275 \\
PIGF (ng/mL) & 6.14 (4.436, 6.58) & 5.99 (4.45, 7.29) & 5.61 (4.74, 6.6) & 4.81 (4.48, 7.15) & 0.745 & 0.863 \\
Tie-2 (ng/mL) & 8.99±2.34 & 9.92±2.89 & 11.26±2.72 & 8.47±2.41 & 2.816 & 0.045 \\
VEGF (ng/mL) & 168.41 (90.86, 327.61) & 83.15 (50.34, 200.11) & 156.24 (117.94, 239.03) & 71.68 (40.74, 234.95) & 4.144 & 0.246 \\
VEGF-C (ng/mL) & 3.76 (1.69, 7.58) & 4.75 (3.72, 9.79) & 6.57 (5.45, 7.82) & 5.31 (3.87, 6.46) & 3.281 & 0.350 \\
VEGF-D (ng/mL) & 18.40 (14.86, 30.31) & 31.92 (26.88, 46.75) & 26.43 (23.64, 36.74) & 24.98 (17.56, 34.74) & 10.433 & 0.015 \\
bFGF (ng/mL) & 14.21 (7.52, 23.18) & 4.32 (2.88, 7.42\textsuperscript{▲}) & 3.23 (1.96, 5.59\textsuperscript{▲}) & 3.20 (2.20, 5.30\textsuperscript{▲}) & 15.861 & 0.001 \\
MMP-3 (ng/mL) & 24.74 (17.96, 51.67) & 36.08 (19.01, 54.34) & 22.03 (14.84, 35.57) & 33.31 (15.86, 41.44) & 5.346 & 0.148 \\
MMP-1 (ng/mL) & 4.98 (3.80, 7.50) & 3.93 (1.94, 7.73) & 2.90 (1.72, 4.50) & 5.80 (3.37, 10.73) & 5.472 & 0.140 \\
MMP-7 (ng/mL) & 2.11 (1.55, 5.02) & 2.86 (1.99, 3.40) & 2.68 (1.64, 4.16) & 3.06 (2.02, 5.03) & 0.864 & 0.834 \\
TRAIL (pg/mL) & 82.28 (57.26, 121.38) & 93.86 (75.98, 140.34) & 98.56 (84.51, 114.28) & 89.96 (61.04, 124.94) & 2.324 & 0.508 \\
Mesothelin (ng/mL) & 25.65 (17.81, 34.84) & 24.10 (17.89, 30.54) & 27.20 (15.40, 30.27) & 21.96 (18.94, 28.50) & 0.688 & 0.876 \\

Note: \textsuperscript{▲}: significance comparing with RS\textsubscript{3}PE patients with malignancy, adjusted P<0.05.

RS\textsubscript{3}PE: Remitting seronegative symmetrical synovitis with pitting edema. Flt-1: fms-like tyrosine kinase 1. VEGF: vascular endothelial growth factor. PIGF: placental growth factor. bFGF: basic fibroblast growth factor. MMP: matrix metalloproteinase. TRAIL: tumor necrosis factor related apoptosis inducing ligand.

**Table 4. Risk factors for malignancy in RS\textsubscript{3}PE by logistic models**

| Variables | univariate analysis | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | B | OR (95%CI) | P | B | OR (95%CI) | P | | |
| Male | 0.411 | 1.508 (0.317 - 7.177) | 0.606 | | | | | |
| Bilateral pitting edema of hands | -2.61 | 0.074 (0.006 - 0.968) | 0.047 | -1.255 | 0.285 (0.035 - 2.320) | 0.068 | | |
| Good response to prednisolone | -3.232 | 0.039 (0.005 - 0.311) | 0.002 | -1.967 | 0.140 (0.017 - 1.182) | 0.071 | | |
| bFGF\textsubscript{10ng/ml} | 2.651 | 14.084 (2.421 - 83.332) | 0.003 | 2.686 | 14.667 (2.029 - 106.038) | 0.008 | | |

RS\textsubscript{3}PE: Remitting seronegative symmetrical synovitis with pitting edema. bFGF: basic fibroblast growth factor.
Figure 1

ROC curve for bFGF in predicting malignancy in patients with RS3PE. ROC: Receiver Operating Characteristic. bFGF: basic fibroblast growth factor. RS3PE: Remitting seronegative symmetrical synovitis with pitting edema.