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Literature Review

RS3PE as Paraneoplastic Rheumatic Syndrome: A Brief Overview and Review of Case Series

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ABSTRACT

Background: RS3PE stands for remitting seronegative symmetrical synovitis with pitting edema thus described in some literature worldwide as a group of symptoms or a syndrome and first described by McCarty in 1985. RS3PE is also known as a rare form of rheumatology pathologic condition correlates with inflammatory arthritis. In past years, the diagnosis of RS3PE should raise the clinician suspicion of the more aggressive possibility of underlying malignancy. Rheumatology and malignancy can share some of its symptoms in various ways, especially in the musculoskeletal system as the main rheumatology focus. **Methods:** Literature review is the used method that focused on publication between January 2011 to 2020 to keep up with the current medical science, which is done using certain keywords. **Discussion:** There is a plethora of literature describing paraneoplastic syndrome and its relation with underlying malignancy, especially prostate and lung adenocarcinoma. RS3PE itself is closely related to VEGF either its idiopathic form or paraneoplastic form; thus, the clinical feature appears similar. In terms of malignancies, VEGF acts as a key role in its pathology as an important growth factor because of VEGF nature as a potent angiogenic molecule. In some malignancies, the VEGF level also appears to be higher than normal, thus suggesting an explanation of paraneoplastic syndrome's nature. **Conclusion:** RS3PE has been strongly correlated with several malignancies mostly prostate cancer; thus should raise the awareness of clinician its signs and symptoms exist in a ce1rtain risky group even if the "pure" form of RS3PE exists.

Keywords: malignancy, paraneoplastic syndrome, rheumatology, RS3PE

ABSTRAK

Latar Belakang: *RS3PE merupakan singkatan dari* remitting seronegative symmetrical synovitis with pitting edema *sehingga dideskripsikan pada berbagai literatur di seluruh dunia sebagai kumpulan gejala atau sindroma yang pertama kali disebutkan oleh McCarty pada tahun 1985. RS3PE juga diketahui sebagai bentuk kondisi reumatologi patologis yang berkorelasi dengan artritis inflamatorik. Beberapa tahun terakhir, diagnosis dari RS3PE harus meningkatkan kecurigaan seorang praktisi kesehatan terhadap keganasan yang melatarbelakangi. Reumatologi dan keganasan juga memiliki beberapa kesamaan perihal gejala dalam bentuk yang berbeda-beda terlebih pada sistem muskuloskeletal sebagai fokus utama reumatologi.* ***Metode:*** *Tinjauan pustaka merupakan metode yang digunakan dan berfokus pada publikasi pada rentang waktu Januari 2011 hingga Desember 2020 sehingga penulisan manuskrip ini masih berdasarkan pengetahuan medis yang terbarukan dan dilakukan menggunakan beberapa kata kunci.* ***Pembahasan:*** *Cukup banyak manuskrip yang telah diterbitkan untuk mendeskripsikan sindroma paraneoplastik dan korelasinya terhadap suatu keganasan. RS3PE, sebagai suatu sindroma paraneoplastik telah dilaporkan oleh berbagai praktisi kesehatan seluruh dunia mengenai korelasinya tehadap beberapa patologi keganasan terutama pada organ prostat, paru, dan kolorektal. RS3PE sendiri erat dikaitkan dengan VEGF baik bentuk idiopatiknya ataupun bentuk paraneoplastiknya. Perihal keganasan, VEGF memiliki peranan yang cukup vital dalam patologinya terkhusus pada faktor pertumbuhan oleh karena sifat dari VEGF sebagai molekul angiogenik potensial. Pada beberapa keganasan, nilai VEGF ditemukan lebih tinggi daripada populasi normal sehingga diduga, menjelaskan penyebab dari suatu kejadian sindroma paraneoplastic.* ***Kesimpulan:*** *RS3PE telah dikorelasikan dengan erat terhadap beberapa keganasan terutama kanker prostat dan kanker kolorektal dengan jumlah yang lebih sedikit sebagai etiologi dari RS3PE sebagai suatu sindroma paraneoplastik walaupun bentuk idiopatiknya ada.*

Kata Kunci: keganasan, reumatologi, RS3PE, sindroma paraneoplastik
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INTRODUCTION

RS3PE stands for remitting seronegative symmetrical synovitis with pitting edema thus described in some literature worldwide as a group of symptoms or a syndrome and first described by McCarty in 1985. Acute-onset, tendency to affect the elderly especially male, respond rapidly to corticosteroid treatment even at the low dose, absence of bony erosions on the radiograph, and most importantly always appear to be a rheumatoid factor (RF) negative are some feature of this syndrome.[1-4] RS3PE is also known as a rare form of rheumatology pathologic condition correlates with inflammatory arthritis. Nowadays, current pathology including the pathogenesis and pathophysiology of the syndrome remains unclear and poorly understood.[5]

The sign and symptoms of RS3PE are strongly associated with other pathologic condition such as polymyalgia rheumatic (PMR) and rheumatoid arthritis (RA) but also correlates with other rheumatological condition such as spondyloarthritides and associated condition, amyloid arthropathy, crystal-induced arthritis, mainly articular chondrocalcinosis, Sudeck's atrophy, mixed connective tissue disease (MCTD) or Sharp's syndrome, and sarcoidosis.[1,3,6] As it definition, the symptoms of RS3PE is the pitting edema on the limb (dorsum of the hand is more common than dorsum of the feet) and symmetrical polyarthritis as the hallmark of the syndrome. In past years, the diagnosis of RS3PE should raise the clinician suspicion to the more aggressive possibility of underlying malignancy as RS3PE can also appear in the form of paraneoplastic syndrome besides its "pure" form.[1,4-9]

Rheumatology and malignancy can share some of its symptoms in various ways especially in the musculoskeletal system as the main rheumatology focus. In other words, malignancy can induce some of the rheumatic symptoms as its clinical manifestation although the symptoms appear to be a trivial one and distant from the main affected tissue or organ.[10-11] A clinician can consider someone having a paraneoplastic syndrome associated with rheumatic symptoms when its affected musculoskeletal symptoms appear simultaneously and no longer than one year. There are several rheumatic conditions considered as a paraneoplastic syndrome such as paraneoplastic arthritis (PA), palmar fasciitis, and polyarthritis syndrome (PEPAS), paraneoplastic vasculitis, hypertrophic osteoarthropathy (HOA) and also RS3PE.[10-12] Some of the more common diagnoses of the rheumatic conditions including dermatomyositis (DM), PMR, Sjogren's syndrome, scleroderma, and vasculitides also appear to be related to some cases of malignancy even there is some diversity in some international studies regarding this information. The diagnosed malignancy is known to involve multi-system. Also, there is a massive variation between underlying malignancy and manifested pathology with adenocarcinoma as the most commonly diagnosed malignancy in rheumatologic patients.[11,13-16]

The exact mechanism of the underlying relation between paraneoplastic rheumatic syndrome and underlying malignancy has been extensively hypothesized.[11] Cancer-induced auto-immunity, several unique auto-antibodies in certain rheumatic condition, e.g., anti-RNAP III in scleroderma and TIF1γ in DM, genetic alteration of autoantigen as the source of the inflammatory reaction, and also toxins produced by the underlying malignancy is several known theories to explain the distinction of manifested symptoms no exception in RS3PE. It's believed, the symptoms of either paraneoplastic syndrome or some cases of rheumatic condition will subside if the underlying malignancy is treated well or even from symptomatic treatment such as low-dose glucocorticoid.[17-19]

METHODS

The literature review is the used method in this literature writing. The source of the literature consists of relevant journal and manuscript that published between 2011 and 2020 using some keywords such as "RS3PE," "Paraneoplastic Syndrome," "Rheumatological Condition," and "Malignancy,". The writer uses ScienceDirect, PubMed, Google Scholar dan ClinicalKey as the search engine in order to search related manuscripts. The used inclusion criteria are full-text manuscript and relatively new manuscript for at least the last ten years. The inaccessible manuscript, a relatively old manuscript is the used exclusion criteria in this literature review manuscript.

DISCUSSION

As mentioned earlier, RS3PE tends to occur in the elderly population and male gender even if there is recent literature mentioned there is an unusual case of RS3PE occurred in a relatively young person.[2,20] There is a strong correlation between RS3PE and other rheumatic conditions especially EORA (Elderly-Onset Rheumatoid Arthritis) and PMR as its most affected population is the elder. Pitting edema at the upper or lower (less common) extremity, mild symmetrical synovitis, and negativity to RF tests are the most clinically significant features to differentiate these closely related pathologies.[7] Radiographic investigation of RS3PE affected person also shows no juxta-articular erosion as it's heavily featured in RA. The symmetrical involvement characteristic of RS3PE is accepted worldwide and considered its pathognomonic feature until some reported cases mention unilateral involvement of RS3PE cases. However, all reported cases were associated with neurological deficits such as stroke (hemiplegia) or brachial plexus palsy and the affected limb is contralateral to the side of the affected neurological deficit limb.[2,4,21]

Therefore, an neurological impairment condition of a limb was shown to be not affected by RS3PE. This condition appears to be closely related to RS3PE pathogenesis that somehow remains unclear but the hypothesized theory shows the role of VEGF (Vascular Endothelial Growth Factor) as the most commonly accepted theory. VEGF is a potent vasodilator and able to increase vascular permeability thus explain the pitting edema or polysynovitis feature of RS3PE. [4,12,20-21]

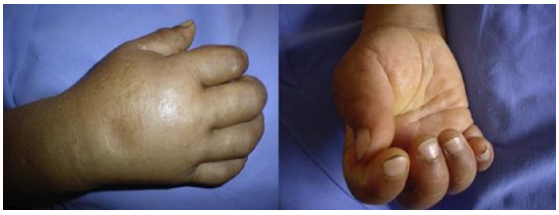

Figure 1. Pitting edema of the hands, synovitis, and loss of ability to grip which marked the diagnosis of RS3PE and descrive its sign and symptoms thoroughly.[7]

RS3PE is not always used as a single clinical diagnosis because it is also categorized as one of many paraneoplastic rheumatic syndromes related to the underlying malignancy with multi-system involvement.[19] There are so many reported cases regarding RS3PE as a paraneoplastic syndrome with variated malignancy from hematological malignancies such as non-Hodgkin's lymphoma, leukemia, and myelodysplastic syndrome to solid tumor including adenocarcinoma of the ovaries, and other associated malignancies from the gastrointestinal tract, lung, urinary tract, etc.[7]

Sakamoto *et al.* in 2017 reported a case of a person suffered from lung adenocarcinoma with RS3PE as its paraneoplastic syndrome that subsides rapidly after gefitinib therapy started by 28 days and achieve complete remission for either its underlying malignancy and RS3PE after 4 years.[2]

Sarkar *et al.* in 2018 stated a case of RS3PE with gastric carcinoma proofed by post-mortem gastric-biopsy. The patient stated the symptoms of its RS3PE had started for one month before the hospital admission as a painful hand with fluctuating in severity accompanied by constant increasing swelling of the dorsum of both hands. The laboratory test was done with a negative outcome for RF and an increase in serum ESR level (Erythrocyte Sedimentation Rate). The end of this case is patient passed away after having a massive melena two days after.[22]

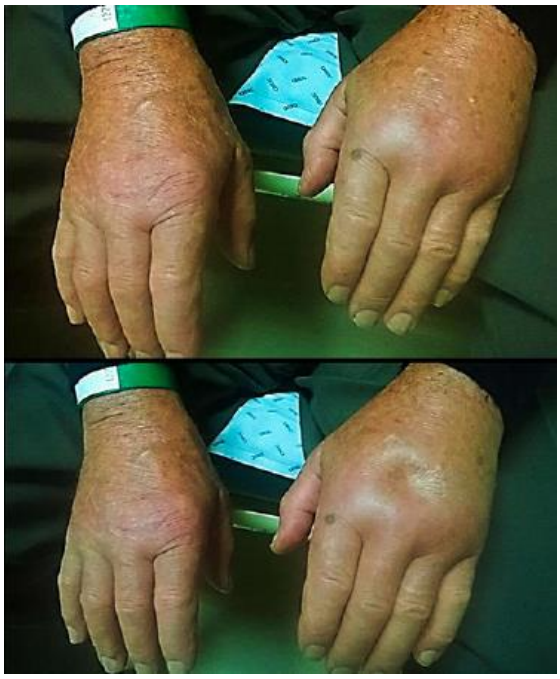

Figure 2. Edema or sweilling of the dorsum of both hand which can be found in a person with an active RS3PE syndrome. The person in the figure was diagnosed with adenocarcinoma of the caecum which exhibited RS3PE as its paraneoplastic syndrome.[23]

Pratas *et al.* published a case report manuscript in 2018 about patients in mid-2015 with adenocarcinoma of the caecum that presents with RS3PE as its paraneoplastic syndrome. As in other RS3PE cases, the patient was having bilateral or symmetrical polyarthralgia of the metacarpophalangeal and proximal interphalangeal joints and pitting edema of the dorsum of the hand accompanied by 6/10 pain with exacerbations event with movement. The patient was given prednisolone for one month before the patient underwent an operative procedure regarding its condition (hemicolectomy). There is neither neoplastic nor RS3PE syndrome relapse for three years after.[23]

Puerto *et al.* in 2013 reported another two cases of RS3PE with one this case reported RS3PE as a paraneoplastic syndrome from an 81-year-old man diagnosed with PCa (Prostate Cancer) before hospital admission. The clinical feature is no different from reported cases stated earlier. Therefore, the patient treated with low-dose glucocorticoid (prednisone 5 mg/day) and the patient achieve its clinical improvement until 13 months later.[24]

Another case report literature shows a case of angioimmunoblastic T-cell lymphoma preceded by RS3PE as its paraneoplastic syndrome. Tabeya *et al.* in 2013 mentioned the correlation of the underlying malignancy of a 76-year-old man and its high VEGF serum which the literature said was 572 pg/ml and perhaps being the main cause of the RS3PE syndrome. Tabeya *et al.* also suspected the high VEGF level is originated by lymphoma cells as it's expressing VEGF-A thus inducing the paraneoplastic syndrome. The patient responds well to glucocorticoid pulse therapy; although an underlying malignancy caused it, the patient was also given chemotherapy during hospitalization. Respond to certain glucocorticoid therapy can identify the etiology of RS3PE syndrome at some point. RS3PE patients with relative resistance to glucocorticoid therapy should be suspected for malignancy as its etiology.[25]

A recent case report from Yajima *et al.* in 2020 about manifested RS3PE syndrome inpatient with another prostatic carcinoma (PCa) showed that paraneoplastic syndrome achieves a complete remission state after the operative procedure or surgical resection is done. Previously, this 77-years-old patient

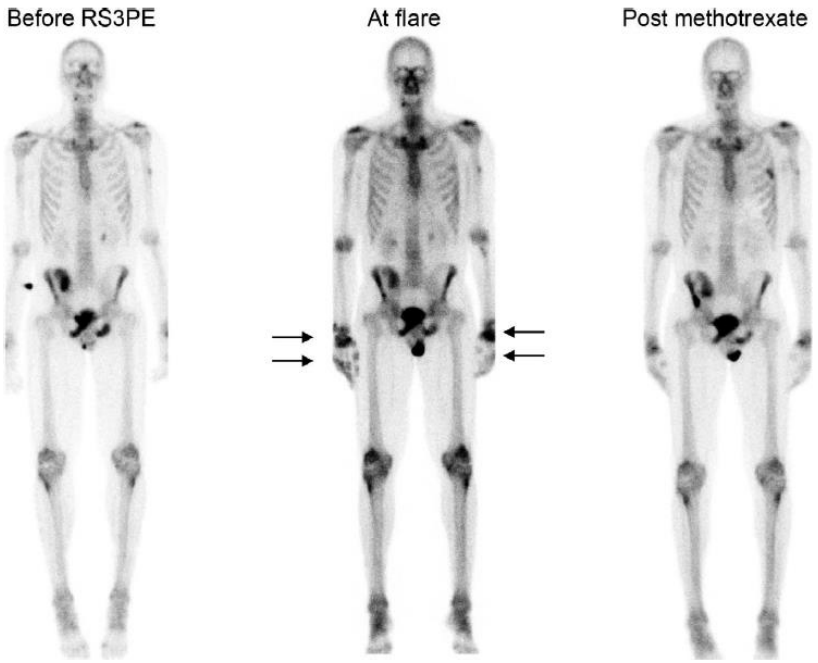

Figure 3. Bone scintigraphy analysis of a person before the development of the RSEP3 (left), at the time of RS3PE flare (middle), and 4 months after receiving methotrexate as his therapeutic therapy regarding its underlying malignancy of musculoskeletal system which showed a remission of the symptoms (right). The high signal from the right hemipelvis, both ischial tuberosities, and several left ribs are the result from the underlying malignancy and metastases thus does not correlate directly toward the workup of RS3PE activity which staged by the signal from both hands specifically wrist and metacarpophalangeal joint.[27]

was diagnosed with PCa two months before the RS3PE syndrome appeared. The manifested symptoms are arthralgia in both shoulders and knees with pitting edema of both hands and feet. Similar to the case presented by Pratas *et al.*, the patient was given low dose prednisolone (15 mg/day) which showed improvement in the paraneoplastic symptoms. But as mentioned earlier, the patient achieves the complete remission of either PCa symptoms or its paraneoplastic syndrome after the surgical procedure.[26]

The most recent case report was published by Kim *et al.* in May 2020 about a 59-years-old man diagnosed with metastatic prostate cancer to the musculoskeletal system (right pubic ramus and left ischiopubic junction in this case series). Similarly, with other reported cases, the patient presented with abruptly onset pain and swelling in his right hand which the symptoms appeared to be self-resolved over a few days. The symptoms were suggested to be its paraneoplastic syndrome originated from its underlying malignancy and also mentioned to interfered with his daily life greatly due to the inability to make a fist. Antinuclear antibody, RF, and anti-CCP were also appeared to be negative. At the end of the report, the cancer was still progressing thus he received radium-223 therapy with no further mention of his paraneoplastic symptoms.[27]

Other cases about RS3PE posed as a paraneoplastic syndrome of underlying malignancies showed an almost similar clinical presentation and characteristic to achieve complete remission. Silte *et al.* in 2014 reported a case of RS3PE with another PCa patient[28], Emamifar *et al.* reported another almost similar case in 2016[29], Sarkar *et al.* previously also had reported a rare association of RS3PE syndrome manifested in a female patient

with phyllodes tumour of breast[30], another case of RS3PE appeared in female population even if its nature to be closely related to male population was presented by Ohe in 2014 about a case of a patient with breast carcinoma which presented with an RS3PE syndrome[31], Dhingani *et al.* also reported another case of RS3PE syndrome manifested in a patient with adenocarcinoma of the lung[32], and the last series of a case report that will be mentioned in this paper is a reported case by Salcido-de Pablo *et al.* in 2014 about another elderly patient with malignancy (colon cancer) and RS3PE as its paraneoplastic syndrome.[33]

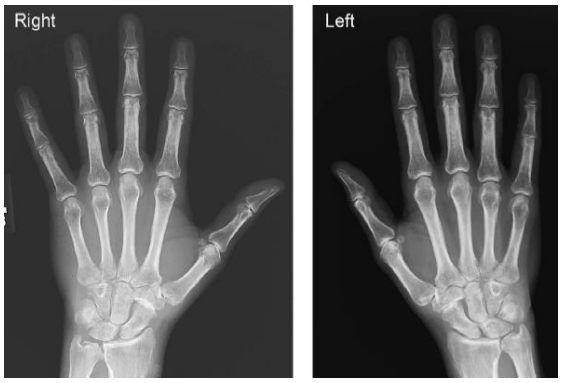

Figure 4. Posterior-anterior (PA) radiographs of the hands bilaterally in the flaring stage of the RS3PE which showing the abcence of the bony erosive change unlike rheumatoid arthritis or several seropositive rheumatologic condition.[7]

There are many published works of literature worldwide especially in the last ten years regarding either stand-alone studies or case reports of RS3PE and its correlation with other pathologies including malignancies. The conclusion of the 12 case reports previously mentioned is the patient with RS3PE as its paraneoplastic syndrome resulting from underlying malignancy appears to be closely related to its etiology. Whether its symptoms or remission. Thus, the best treatment for paraneoplastic symptoms is the etiologic treatment focused on underlying malignancy such as surgical resection or chemotherapy.[2,22-33]

As mentioned earlier, the pathology of RS3PE is closely related to VEGF either its idiopathic form or paraneoplastic form. VEGF acts as a potent angiogenic and vasogenic molecule thus able facilitating hypervascularity and increasing vascular permeability so caused synovitis and sub-cutaneous edema respectively.[34-35]

In terms of malignancies, VEGF acts as a key role in its pathology as an important growth factor because of VEGF nature as a potent angiogenic molecule. High level or over-expression of VEGF can also be found in other rheumatological pathologies such as rheumatoid arthritis or psoriasis. Induction of vascularization for the cancer cells is provided by VEGF at a high level thus forming a neo-vascularization to supply the cancer cells. Because every tissue in the body certainly needs vascularization as a provider of the nutrient flow, VEGF is known to be expressed in most tumor cases, especially malignancies in every multi-system possible and certainly highly correlates with its progression. VEGF expression also has a higher association with digestive system cancer such as gastric cancer, colorectal cancer, pancreatic cancer, etc. Although the level of VEGF in other malignancies includes prostate and breast cancer should never be neglected.[36-39] High level of VEGF condition in person with malignancy caused the possibility of its con dition to induce some paraneoplastic syndrome including or especially RS3PE.[10,12,18-19,27]

Besides RS3PE pathology, several genetic factors are known to be closely related to the emergence of the syndrome in some persons thus explaining not every person with certain malignancy especially some pathology with high VEGF level will develop RS3PE at its progression. HLA-B7, HLA-A2, and HLA-Cw7. These specific genes also explain the reason behind more significantly and certain relative tendencies regarding its musculoskeletal involvement in some paraneoplastic syndromes especially RS3PE which presumed correlated with the association between several HLA

genes and several rheumatologic conditions. Nevertheless, Paik *et al.* in 2019 mentioned the existence of a specific HLA gene namely HLA-DRB1 does not correlate with the occurrence of RS3PE in a person as its absence is one of the features of the genetic workup in an RS3PE patient. Eventually, the occurrence of RS3PE in a person is resulted from several and certain factors whether internal or external or even resulted from an underlying malignancy which also proceeded by another risk factor of each pathology.[5,21,40-42]

CONCLUSION

RS3PE has been strongly correlated with several malignancies mostly prostate cancer and colorectal cancer with a fewer number of reported as its etiologies even the primary or "pure" form of RS3PE exists. VEGF is known as a causal substance for RS3PE syndrome, which is proven by some studies the high level of VEGF is found either in primary RS3PE patient or patient with malignancy, which presented RS3PE as its paraneoplastic syndrome.

RECOMMENDATIONS

Further development and study regarding the correlation or association of several malignancies with the occurrence of RS3PE as its paraneoplastic syndrome should be done in the future thus justify the clinician awareness. The understanding and comprehension of the nature of RS3PE as a paraneoplastic syndrome should lead to the advanced workup which able to detect, thus preventing the progression of underlying neoplastic even if the primary or "pure" form of RS3PE remain.

The necessity toward a broad-type systematic review and meta-analysis publication remain high as the most published literature focused on RS3PE are dominated by case study publications thus only recap the condition of one or several patients which unable to explore several potential factors on a larger scale, e.g., assuring its correlation with a more specific neoplastic rather than only a suggestion of the VEGF's role which upregulated in several malignancies, or elaborate the correlation between a specific risk factor of a specific malignancy which certainly exhibited a different factor one to each other thus obscured another risk factor for the development of RS3PE, or even explaining the exact and comprehensive pathology which remain unclear until now.

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