Remitting Seronegative Symmetrical Synovitis with Pitting Edema Syndrome: Followup for Neoplasia

ELIZABETH B. RUSSELL

ABSTRACT. ***Objective.*** To investigate whether the remitting seronegative symmetrical synovitis with pitting edema (RS_3PE) syndrome may represent a paraneoplastic disorder in a significant percentage of cases.

Methods. Patients diagnosed with RS_3PE syndrome at the Medical College of Wisconsin before 1995 were telephoned and asked about their rheumatologic course since initial diagnosis of RS_3PE and whether they had been diagnosed with any cancer. If so, permission was obtained to review tissue pathology. Criteria used for diagnosis of RS_3PE syndrome included sudden onset of painful diffuse swelling of both hands associated with pitting edema of the dorsa of the hands without other synovitis or evidence of disease, negative rheumatoid factor, absence of radiologic abnormalities, and resolution within 6–12 months without sequelae. Data from the national SEER databank on population incidence of cancers in the appropriate sex, age, and ethnic groups for the years under study were used to assess relative risk for cancer.

Results. There were 10 patients for whom followup data were available. Four had a cancer diagnosed following recognition of the RS_3PE syndrome; 1 patient developed non-Hodgkin's lymphoma initially diagnosed as hairy cell leukemia after 4 years; 1 developed acute lymphocytic leukemia with hyperdiploidy after 14 years; 1 was diagnosed with male breast cancer after 2.5 years; and 1 developed squamous cell lung cancer 12 months after RS_3PE diagnosis. SEER data project an estimated rate of 2–3 cancers in a similar group of 10 patients of the same sex, age, and time period for this geographic area.

Conclusion. The small sample size in this longterm followup precludes extrapolation to larger populations but suggests that there may be a slightly higher than expected rate of neoplasia in patients diagnosed with RS_3PE syndrome. The interval between onset of RS_3PE syndrome and diagnosis of cancer was fairly long, indicating that patients should be monitored for neoplasia with prudent age and sex specific surveillance for an extended period after diagnosis with RS_3PE. (J Rheumatol 2005;32:1760–1)

Key Indexing Terms:
RS_3PE LONGTERM FOLLOWUP NEOPLASIA

Since the original description by McCarty, *et al* in 1985[1,2], over 150 cases of remitting, seronegative, symmetric synovitis with pitting edema (RS_3PE syndrome) have been reported. This syndrome of pain, swelling, and pitting edema of the hands has been reported primarily in elderly males. Patients present with sudden (over hours to days) onset of an extreme degree of pitting edema of the soft tissues of the dorsa of the hands, giving the hands an appearance of "boxing gloves." In addition, there is associated synovitis of the small joints and tenosynovia, confirmed by magnetic resonance imaging studies of such patients[3,4]. Laboratory work reveals an elevated erythrocyte sedimentation rate but few other consistent abnormalities, and radiographs are negative for any erosive arthritis. Originally described as benign, it responds to hydroxychloroquine or low dose steroid treatment and remits without sequelae, although subclinical flexion contractures at proximal interphalangeal joints have been observed[1].

Since the original report, additional reports of patients have raised the possibility that the RS_3PE syndrome may be a paraneoplastic disorder[5-9]. These case reports have noted a temporal correlation between the appearance of these musculoskeletal symptoms and the development of neoplasia. The time lapse between these events has been quite variable, ranging between months to over a year[7]. There has been no histological continuity between cases, and both solid tumors and hematogenous malignancies have been reported[7]. More interestingly perhaps are intriguing reports of resolution of the musculoskeletal symptoms of RS_3PE in cases where a cancer has been removed[8,9]. In cases where the temporal association is quite close, an apparent causal relationship is intuitively suggested.

This longterm followup study was designed to accumu-

From the Division of Rheumatology, Department of Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin, USA.

E.B. Russell, MD.

Address reprint requests to Dr. E.B. Russell, 8701 Watertown Plank Road, Milwaukee, Wisconsin, 53226.

Accepted for publication May 9, 2005.

late further data to either support or refute the hypothesis that the RS_3PE syndrome may represent a paraneoplastic disorder in a significant percentage of cases.

MATERIALS AND METHODS

Study patients. A standard questionnaire was developed and approved by the Institutions Review Board of the Medical College of Wisconsin. Patients diagnosed with RS_3PE syndrome at this institution before 1995 were telephoned and asked about their rheumatologic course since the initial diagnosis of RS_3PE and whether they had been diagnosed with any cancer. If so, permission was obtained to review tissue pathology.

Analysis. Criteria used for diagnosis of RS_3PE syndrome included sudden onset of painful diffuse swelling of both hands associated with pitting edema of the dorsa of the hands without other synovitis or evidence of disease, seronegativity for rheumatoid factor, absence of radiologic abnormalities, and resolution within 6-12 months without sequelae.

Data from the Surveillance Epidemiology and End Results database of the US National Cancer Institute (SEER) on population incidence of cancers in the appropriate sex, age, and ethnic groups for the years under study were used to assess relative risk for cancer[10].

RESULTS

Followup data were available for 10 patients from an original cohort of 25. The remaining 15 patients could not be located for followup. Two of these 15 were reported by family to have possibly died of heart disease but this could not be substantiated. No data were available on the other 13 patients.

Of the 10 patients contacted, the span of years representing time since diagnosis of RS_3PE ranged from 1 to 19. The mean age at presentation was 68 years (range 45-81). All but one had no recurrence of their RS_3PE symptoms after the initial presentation. One patient had a single reoccurrence of sudden pain and diffuse swelling of both hands identical to that of his initial presentation 19 years earlier. This was confirmed by the patient's rheumatologist who treated the patient with bilateral intraarticular metacarpophalangeal steroid injections. The patient had a prompt response and all symptoms resolved in 3 months without subsequent relapse.

Cancer was diagnosed following RS_3PE syndrome in 4 of 10 patients for whom data were available (Table 1). One patient developed non-Hodgkin's lymphoma, initially diagnosed as hairy cell leukemia, 4 years after presenting with RS_3PE syndrome. He is alive after receiving chemotherapy. The second patient developed acute lymphocytic leukemia with hyperdiploidy 14 months after presenting with RS_3PE syndrome. He had been treated with low dose prednisone with good response. Steroid therapy was being tapered when the cancer was diagnosed, and he died 6 months later. The third patient presented with RS_3PE syndrome that responded to low dose steroids and was diagnosed 2.5 years later with male breast cancer. His death 2 years later was attributed to cancer. The fourth patient developed squamous cell lung cancer 12 months after being diagnosed with RS_3PE syndrome and died 2 years later. His case was complicated by a concurrent diagnosis of lupus with nephritis and a prior history of colon cancer.

SEER data give incidence figures projecting an expected rate of 2 to 3 cancers in a similar group of 10 patients of the same sex, age, and time period for this geographic area.

Table 1. Cancers diagnosed in 4 male patients following presentation with RS_3PE syndrome.

Age at Diagnosis of RS_3PE, yrs	Cancer	Time Between RS_3PE and Cancer, mos
80	Lymphoma (non-Hodgkins)	48
82	Leukemia	14
71	Breast cancer	30
70	Lung cancer	12

DISCUSSION

The small number of patients in this longterm followup study precludes extrapolation to larger populations but suggests that there may be slightly higher than expected rate of neoplasia in patients diagnosed with RS_3PE syndrome. The interval between onset of RS_3PE syndrome and diagnosis of cancer was fairly long suggesting that such patients should be monitored for neoplasia with prudent age and sex specific surveillance for an extended period, if not indefinitely. Prospective followup studies on larger cohorts would help clarify longterm risk of neoplasia in patients with RS_3PE syndrome.

ACKNOWLEDGMENT

The author thanks Dr. D. McCarty for his assistance over these years.

REFERENCES

1. McCarty D, O'Duffy D, Pearson L, Hunter J. Remitting seronegative symmetrical synovitis with pitting edema. RS3PE syndrome. JAMA 1985;254:2763-7.
2. Russell E, Hunter J, Pearson L, McCarty D. Remitting seronegative symmetrical synovitis with pitting edema-13 additional cases. J Rheumatol 1990;17:633-9.
3. Cantini F, Salvarani C, Olivieri I, et al. Remitting seronegative symmetrical synovitis with pitting oedema (RS3PE) syndrome: a prospective follow up and magnetic imaging study. Ann Rheum Dis 1999;58:230-6.
4. McGonagle D, Pease C, Marzo-Ortega H, O'Connor P, Emery P. The case for classification of polymyalgia rheumatica and remitting seronegative symmetric synovitis with pitting edema as primarily capsular/entheseal based pathologies. J Rheumatol 2000;27:837-40.
5. Tada Y, Sato H, Yoshizawa S, et al. Remitting seronegative symmetrical synovitis with pitting edema associated with gastric carcinoma. J Rheumatol 1997;24:974-5.
6. Sibilia J, Friess S, Schaeverbeke T, et al. Remitting seronegative symmetrical synovitis with pitting edema (RS3PE): a form of paraneoplastic polyarthritis? J Rheumatol 199;26:115-20.
7. Cantini F, Salvarani C, Olivieri I. Paraneoplastic remitting seronegative symmetrical synovitis with pitting edema. Clin Exp Rheum 1999;17:741-4.
8. Cantini F, Olivieri I, Salvarani C. More on remitting seronegative symmetrical synovitis with pitting edema as a paraneoplastic syndrome. J Rheumatol 1998;25:188-9.
9. Vinci M, Malaguanera L, Pistone G. RS3PE and ovarian cancer. Ann Rheum Dis 2001;60:429-31.
10. Ries L, Wingo P, Miller D, et al. The annual report to the nation on the status of cancer, 1973-1997, with a special section on colorectal cancer. Cancer 2000;88:2398-410.