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반복하여 재발한 류마티스 결절증(nodulosis) 1예

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Rheumatoid Nodulosis with Recurrent Nodules: A Case Report

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Rheumatoid nodulosis, a benign variant of rheumatoid arthritis (RA), is a rare condition characterized by multiple subcutaneous nodules and positive rheumatoid factor in the absence of systemic manifestations or joint disease. Asymptomatic nodules rarely require treatment, and are unlikely to recur after excision, except in cases in which RA develops. Here, we describe an unusual case of recurrent rheumatoid nodulosis in a 42-year-old female presenting with recurrent subcutaneous nodules on the plantar side of her left foot, which caused pain when walking. Nodules were initially excised to control symptoms; however, since the excision, the nodules have recurred twice in the absence of other RA symptoms. (Korean J Med 2015;88:241-245)

Keywords: Rheumatoid nodulosis; Rheumatoid arthritis; Synovitis

INTRODUCTION

Rheumatoid nodulosis is considered to be a variant of rheumatoid arthritis (RA) characterized by the presence of rheumatoid nodules in the absence of definitive synovitis [1]. Development of rheumatoid nodulosis is regarded as a rare condition, with only a handful of cases having been reported in adults [2-4]. Here, we report a case with rheumatoid nodulosis characterized by recurrent nodules on the foot.

CASE REPORT

A 42-year-old female presented with firm, mildly tender recurrent nodules on the plantar side of her left foot. The patient reported foot pain while walking, and an obtuse sensation at the second and third toes since the initial appearance of the nodules

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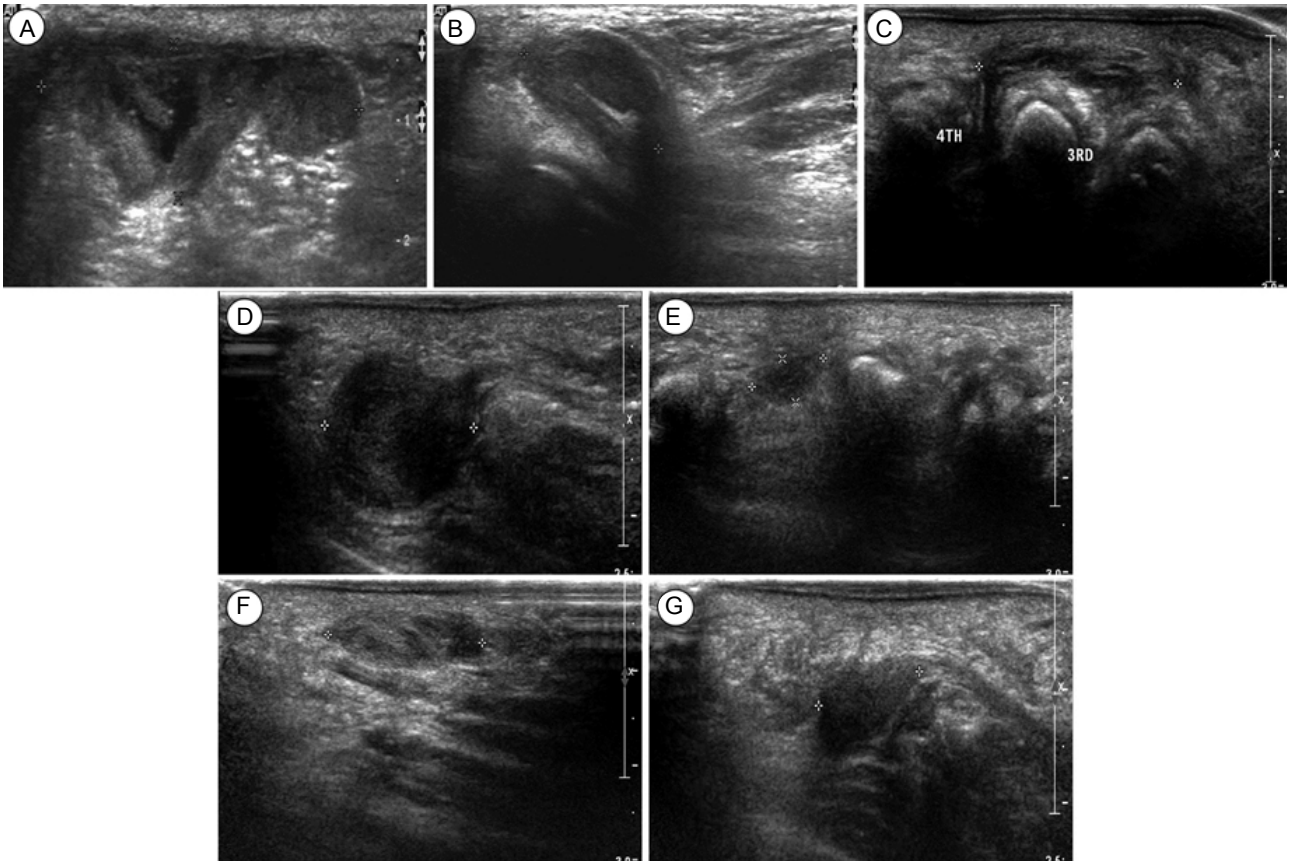

Figure 1. Multiple, well-demarcated subcutaneous masses in the foot were diagnosed by ultrasound at each visit. (A, B) Two masses were seen at the time of first presentation. (A) A multilobulating, contoured, heterogeneous, hypoechoic mass 3.8 × 1.3 cm in size was observed in the lateral aspect of the fifth toe of the left foot. (B) A 1.9 × 1.0-cm hypoechoic mass in the second web space of the left foot. (C) Recurrent masses were demonstrated after excision. A 2.4 × 2.8-cm elongated mass was observed in the third web space and plantar aspect of the second and third metatarsals of the left foot. (D-G) Multiple masses were demonstrated again after the second excision. (D) A 1.8 × 1.8-cm heterogeneous, low echoic mass in the third web space of the right foot. (E) A 0.9 × 0.4-cm mass in the fourth metatarsal web space of the right foot. (F) A 1.8 × 0.6-cm nodule in the lateral aspect of the fifth toe on the right foot. (G) A 1.2 × 0.8-cm nodule in the second metatarsal web space of the right foot.

2 years previously; a previous bout of nodules had been treated by excision, along with the removal of possible ganglion cysts one year prior to presentation. A foot ultrasound revealed two subcutaneous nodules, which were palpated and visible at the second web space and the fifth metatarsophalangeal (MTP) joint area of the plantar aspect of the foot (Fig. 1A and 1B). The nodules were excised to relieve pain, and histopathology confirmed that the diagnosis was compatible with a typical rheumatoid nodule (Fig. 2A). The patient was then referred to the rheumatology department.

There was no remarkable history of trauma, underlying medical conditions, or familial disease. She had experienced migrating joint pain at both shoulders and knees a few years previously, however this pain appeared to be unrelated to the current condition. A thorough physical examination revealed no significant findings, including any signs of active arthritis. Routine laboratory tests, including a complete blood cell count and a chemistry profile including fasting glucose and uric acid (4.6 mg/dL, reference range 2.4-6.0) revealed no abnormalities. Acute-phase reactants, such as erythrocyte sedimentation rate (ESR) (19 mm/h, reference range 0-27) and C-reactive protein (CRP) (0.04 mg/dL, reference range 0.0-0.3) were within normal limit, and hepatitis B and C antibody tests were all negative. Chemistry profiles were checked again at 1 and 4 months, with uric

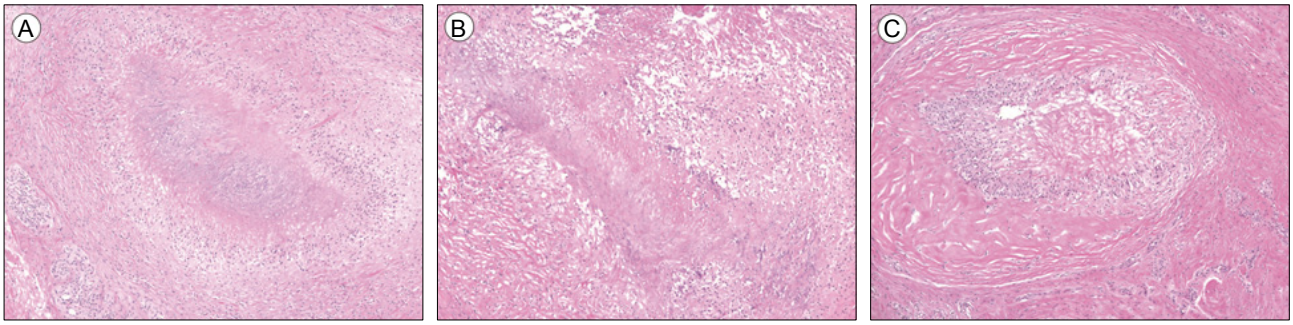

Figure 2. Histologic examinations of the specimens. (A) The specimen of the first excisional biopsy. (B) The specimen of the second, and (C) third excisional biopsy. They revealed multiple nodular lesions composed of a necrotic center with accumulated fibrin, surrounded by inflammatory cells arranged in a palisading fashion. Inflammatory cells were predominantly lymphocytes and histiocytes. These findings were consistent with a rheumatoid nodule (Hematoxylin and eosin stain, 100×).

acid, ESR, and CRP levels all within reference ranges. Serologic tests were positive for rheumatoid factor (RF) (45.4 IU/mL, reference range 0-20) and weakly positive anti-nuclear antibodies; the test for anti-cyclic citrullinated peptide antibodies (ACPA) was unavailable at the time of investigation. Foot radiographs displayed neither signs of arthritis nor detectable cystic bone lesions.

The patient was diagnosed with rheumatoid nodulosis based on nodule histopathology and the lack of synovitis. Disease-modifying antirheumatic drugs (DMARDs) were not prescribed, however a non-steroidal anti-inflammatory drug (NSAID) was prescribed for symptomatic relief.

Following treatment, the patient was lost to follow-up but presented again four years later with recurred nodules in other sites on her left foot. Ultrasonography indicated a subcutaneous nodule at the third web space that extended to the plantar aspect of the second metatarsal head with no erosion or synovial hyperplasia (Fig. 1C). The nodules were again excised, with histopathological analyses confirming a diagnosis of rheumatoid nodules (Fig. 2B). Three years later, she complained of bothersome discomfort in her right foot. Another ultrasound revealed three nodules at the second, third, and fourth web spaces but no signs of arthritis (Fig. 1D-G). ESR and CRP were 45 mm/h (0-27), 0.55 mg/dL (0.0-0.3), respectively. All of the nodules were excised, revealing the same pathology as before (Fig. 2C).

Postoperative chief complaints were the overriding of the second toe to the great toe and a widening of the space between the second and third toes on the right foot. Over the course of the next two years, no new nodules appeared, and RA did not develop based on physical examinations and ultrasonography. The patient refused to undergo additional laboratory testing for RF and ACPA, as there was no joint pain or sign of systemic inflammation.

DISCUSSION

Rheumatoid nodules are among the most common extra-articular features of RA, occurring in ~20% of RA patients [5]. Rheumatoid nodulosis, in comparison, is relatively uncommon, having been reported in only a handful of cases [2-4], with no reports of recurrent episodes of rheumatoid nodulosis in the feet [4].

The term rheumatoid nodulosis was originally introduced to describe cases of rheumatoid nodules in the absence of systemic illness or marked synovitis [1]. After reviewing 24 cases of rheumatoid nodulosis, Couret et al. [3] suggested the following four criteria for diagnosis: (1) Multiple subcutaneous rheumatoid nodules identified by biopsy, (2) recurrent joint symptoms with minimal clinical or radiological involvement, (3) benign clinical course, and (4) no or mild systemic manifestations of RA. The case described here fulfills all four of these criteria, although the nodules were recurrent with the possibility of malignancy.

When a patient presents with palpable nodules in the absence of other clinical symptoms, such as arthritis, it can be challenging for physicians to reach a definitive diagnosis. Excisional bi-

opsy can provide additional information, but is not always appropriate, and can cause unnecessary sequelae. Nodules confined to the feet area, as in this case, may be attributable to gouty tophi or Morton's neuroma; however, none of these conditions were considered a probable diagnosis in this case. Gouty tophi can develop under conditions of prolonged hyperuricemic, and is most commonly seen in males with a history of repetitive acute attacks. Uric acid levels were normal in this premenopausal female patient, and there was no record of such acute attacks in her medical history. Ultrasonographic findings also supported differentiation from tophi or Morton's neuroma in terms of the echogenicity, along with the shape and location of nodules. While tophi are commonly heterogeneous and hyperechoic with poorly defined contours around the MTP joints, Morton's neuroma can be seen as a thickening of the interdigital nerve within the web space, most commonly of the second and third web spaces, typically at the level of the intermetatarsal ligament [6]. Tophi and neuroma were definitely and easily excluded based upon the pathology of biopsied nodules.

Meanwhile, rheumatoid nodules are similar in histopathologic morphology to necrobiosis lipoidica and granuloma annulare, although some differences are now generally accepted [7]. Therefore, clinical findings should be scrutinized to interpret pathologic findings. Necrobiosis lipoidica is characterized by collagen degeneration combined with a granulomatous response involving diffuse dermis [8]. However, as this type of lesion is accompanied by an erythematous or necrotizing skin condition, and is primarily found in diabetic patients, we were able to rule out this condition the present case.

Unlike necrobiosis lipoidica, differentiation of granuloma annulare is more challenging as it often presents as a subcutaneous form grossly resembling that of rheumatoid nodules. Subcutaneous granuloma annulare are characterized by benign inflammatory dermatoses in the deep dermis and subcutaneous tissue and usually appears in children and young adults. It is commonly located on the anterior aspects of the lower legs, hands, head, buttock, and dorsal feet [9], consistent with clinical presentations described here; however, histological finding did not support such a diagnosis. Granuloma annulare are characterized by a pale and mucinous center and tend to be basophilic, compared to rheumatoid nodules, such as the one described here, which exhibit areas of eosinophil degeneration accompanied by abundant fibrin deposition. Serologic tests such as RF are also advised for suspected rheumatoid nodules as the condition may progress to RA.

Rheumatoid nodulosis is an inherently self-limiting disease, which can be symptomatically controlled using standard NSAIDs. However, in cases where the presence of rheumatoid nodules leads to additional disease morbidity, such as when nodules are on present on the hands or feet, more aggressive treatments are necessary. Slow-acting DMARDs or other anti-inflammatory drugs, such as colchicine, hydroxychloroquine, or D-penicillamine may be used to reduce the size of nodules; intralesional glucocorticoid injection and surgical excision also can be performed. Tumor necrosis factor inhibitors were found to be ineffective in these patients, while other, more experimental treatments, such as intralesional fluorouracil injection and intravenous rituximab, have shown some promise [10]. In this case report, excision was performed due to the symptomatic nature of the nodules, along with the patient's preference for surgical treatment.

The localization of recurrent nodules on the feet is an important aspect of this particular case. Considering that such nodules typically appear on the extensor surfaces of the elbow and are generally associated with repetitive traumatic pressure, the recurrence of these nodules may be related to the low-grade, repeated trauma associated with walking, thereby triggering a granulomatous inflammation response, and potentially even provoke the recurrence of subsequent nodules. Regardless of the role trauma played in this individual, the mechanism of RF and its contribution to the development of rheumatoid nodules without synovitis have not been elucidated. Furthermore, it is not known whether DMARDs could be used to prevent symptomatic rheumatoid nodulosis and recurrence in patients without evidence of RA. A single case report describing a patient who developed RA 10 years after the detection of rheumatoid nodules raises the possibility of eventual symptom progression in the individual described here [7]. Extended follow-up periods will be necessary to determine the time period needed to differentiate be-

tween early stages of arthritis and more benign cases of rheumatoid nodulosis.

Based upon these findings, rheumatoid nodulosis could be included in the differential diagnosis of subcutaneous nodules on the feet of patients with positive serology but no active synovitis. Ultrasound can be utilized for an accurate diagnosis, and a confirmatory excisional biopsy is also advisable for follow-up in symptomatic cases.

중심 단어: 류마티스 결절증; 류마티스 관절염; 활막염

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