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ORIGINAL ARTICLE

Clinicopathologic features of rheumatoid nodules: a retrospective analysis

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Abstract

Objectives The clinical and histopathologic features of patients that have been diagnosed with rheumatoid nodules were investigated.

Methods This study included patients with rheumatoid nodules, confirmed by histologic assessment, between 2005 and 2018 at the Hanyang University Hospital. Each patient had a total score of 6 or more according to the American College of Rheumatology criteria.

Results A total of 57 cases were included in this study. The median age of the patients at the time of diagnosis was 57 years (range, 39–70 years). The average duration between the onset of treatment and occurrence of rheumatoid nodule was 11.6 years. Bone erosion was observed in 44 patients (77.2%). Among 57 patients, 56 (98.2%) were treated with disease-modifying anti-rheumatic drugs; most of the patients (87.7%) showed high-positive rheumatoid factor or high-positive anti-citrullinated protein antibodies. The foot, hand, and wrist, in order of decreasing frequencies, were the anatomical sites with the highest occurrence of rheumatoid nodules, whereas, the soft tissue adjacent to the joint, subcutis, dermis, lung parenchyma, and submucosal layer of the supraglottic area, also in an order of highest frequency, were the histological sites with the highest occurrence. Microscopically, central necrobiosis was present in all cases. Stromal fibrosis (96.5%), palisading of histiocytes (82.5%), perivascular lymphocytic infiltration (68.4%), and cleft or cystic degeneration (63.2%) were also observed.

Conclusions A clinicopathological review of cases diagnosed with rheumatoid nodules histologically was performed to confirm characteristics that can help clinicians understand the pathophysiology of the condition and make accurate diagnoses of rheumatoid nodules.

Key Points
- *We reviewed the clinical, imaging, and histologic features of rheumatoid nodule.*
- *The average duration between the onset of treatment and occurrence of rheumatoid nodule was 11.6 years.*
- *Among 57 rheumatoid nodule patients, 98.2% were treated with disease-modifying anti-rheumatic drugs.*

Keywords Rheumatoid nodule · Rheumatoid nodules · Rheumatoid noduloses · Rheumatoid nodulosis

Introduction

A rheumatoid nodule is the most common extra-articular manifestation and characteristic lesion in rheumatoid arthritis (RA) patients. This is mainly manifested as a cutaneous mass; however, it can arise in various non-cutaneous sites such as the lung, tendon, vocal cord, occiput, and sacrum. The diagnosis of rheumatoid nodules is usually determined clinically with typical clinical characteristics without requiring additional diagnostic testing [1]. However, if there is uncertainty in the

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diagnosis, distinct histologic features of rheumatoid nodules should be confirmed by excisional biopsy. Rheumatoid nodules in the lung, which is a commonly affected site of non-cutaneous rheumatoid nodules, can mimic infections such as tuberculosis, or neoplastic diseases [1].

Necrobiosis, with fibrin deposition and palisading epithelioid histiocytes, is a typical histologic feature of rheumatoid nodules. The area of central necrosis contains necrotizing endothelial cells and histiocytes. The outer area tends to show granulation tissues with chronic inflammatory cells and significant stromal fibrosis. Focal vasculitis and occasional giant cells can also be found [1–3]. Overall, the histologic appearance of rheumatoid nodules is representative of an immune-mediated granulomatous process. These surrounding palisading epithelioid histiocytes are antigen-presenting cells testing positive for human leucocyte antigen–DR isotype (HLA-DR) and were found to secrete interleukin (IL)-1, tumor necrosis factor (TNF), interferon, IL-10, IL-15, IL-18, and IL-12 in other studies [4–6].

The incidence rate of rheumatoid nodules in RA patients was about 30–40% in several cohort studies [7]. Smoking, known as a risk factor and local trauma, can affect developing rheumatoid nodules. In some RA patients who received methotrexate (MTX) or leflunomide (LEF) therapy, accelerated rheumatoid nodulosis has been reported [8–10].

The aim of this study was to describe the clinical and histopathologic features of patients that were diagnosed with rheumatoid nodules in one institute.

Material and methods

This study was a retrospective study and included patients who were confirmed by histologic assessment of rheumatoid nodules. There were 58 patients diagnosed with rheumatoid nodule between 2005 and 2018 at Hanyang University Seoul Hospital. Among 58 rheumatoid nodule cases, one case was excluded due to a lack of clinically relevant to the diagnosis of RA. Finally, a total of 57 cases were included in this study. All 57 patients were diagnosed with definite rheumatoid arthritis, for scoring 6 or more according to the American College of Rheumatology (ACR) criteria. In summary, the scores were calculated based on the type and number of joints involved, the elevation of rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA), the elevation of acute-phase reactants, and the duration of symptoms in patients with synovitis [11]. Ziehl–Neelsen staining was used to test for *Mycobacterium tuberculosis* (MTB) and non-tuberculous mycobacteria (NTM). Subsequently, real-time polymerase chain reaction (RT-PCR) confirmed all results to be negative, during diagnosis.

Clinical data including age, gender, smoking history, history of RA medication, interval between diagnosis of RA and occurrence of the rheumatoid nodule, serum levels of autoimmune markers, extra-articular manifestations, and other medical histories were obtained from electronic medical records. The bone erosion of the affected joints in RA patients and data on clinical impression and imaging assessment before histologic diagnosis were also collected.

Hematoxylin and eosin (H&E) stained slides of rheumatoid nodule were carefully reviewed by two pathologists. Histopathologic features were classified according to the presence or absence of the following characteristics: necrobiosis, palisading histiocytes, multinucleated giant cells, perivascular lymphocytic infiltration, stromal fibrosis, cleft or cystic degeneration, peripheral vasculitis, and neutrophil infiltration.

Statistical analysis

Pearson's chi-square ($\chi 2$) test or Fisher's exact test was performed to investigate the correlation of histopathologic features with clinical characteristics, clinical impression, and imaging assessment. In all analyses, two-sided p value < 0.05 was regarded as significant. Data analysis was performed using SPSS software version 25.0 (IBM, Armonk, USA).

Results

Patient characteristics

Of 19,937 RA patients between 2005 and 2018, 57 patients (0.29%) had histologically confirmed rheumatoid nodule. The median age of the patients at the time of diagnosis of rheumatoid nodule was 57 years (range, 39~70 years). The patients were predominantly female (48, 84.2%). The median interval between the onset of treatment for RA and occurrence of the rheumatoid nodule was 12 years (range, − 14 months ~ 31 years). Among 57 patients, there was no current smoker, five (8.8%) were ex-smokers, and the rest of them was never smoker. Bone erosion was observed in 44 patients (77.2%; Table 1). Three patients (5.3%) showed extra-articular manifestations other than rheumatoid nodule. Two were diagnosed with interstitial lung disease associated with RA by high-resolution computed tomography. One patient was diagnosed with mononeuritis multiplex during the follow-up period (Supplemental material 1).

Most of them (50, 87.7%) showed high-positive RF or high-positive ACPA (> 3 times the upper limit of normal, ULN); six patients (10.5%) showed low-positive RF or ACPA (higher than ULN, but ≤ 3 times the ULN). Only one patient tested negative for both RF (less than 15 IU/mL) and ACPA (less than 25 IU/mL). Fourteen patients tested positive for various serum autoimmune markers, such as cryoglobulins (4 cases), anti-SS-A/Ro (4 cases), anti-thyroglobulin (TG, 3 cases), anti-neutrophil

Table 1 Demographics and clinical characteristics of the 57 rheumatoid nodules

Characteristics	Case no. (%)
Age, median (range, year)	57 (39–70)
Sex	
Male	9 (15.8%)
Female	48 (84.2%)
Smoking history	
Never smoker	52 (91.2%)
Ex-smoker	5 (8.8%)
Bone erosion	
Present	44 (77.2%)
Absent	13 (22.8%)
ACR criteria (total score)	
6	10 (17.5%)
7	18 (31.6%)
8	11 (19.3%)
9	2 (3.5%)
10	16 (28.1%)
Serum RF and ACPA	
High RF or high ACPA (> 3 times the ULN)	50 (87.7%)
Low RF or low ACPA (higher than ULN, but ≤ 3 times the ULN)	6 (10.5%)
Negative RF (less than 15 IU/mL) and negative ACPA (less than 25 IU/mL)	1 (1.8%)
Other serum autoimmune markers	
Cryoglobulins	4 (7.0%)
Anti-TG (> 50 IU/mL)	3 (5.3%)
Anti-TPO (> 30 IU/mL)	1 (1.8%)
ANA (> 1:160)	1 (1.8%)
ANCA	2 (3.5%)
Anti-SS-A/Ro (> 10 U/mL)	4 (7.0%)
Anti-Scl-70 (> 10 U/mL)	1 (1.8%)
Anti-SS-B/La (> 10 U/mL)	1 (1.8%)
Medication	
DMARDs	56 (98.2%)
NSAIDs	52 (91.2%)
Steroid	44 (77.2%)
Biologics*	3 (5.3%)
Other immunosuppressive drugs†	4 (7.0%)
Anatomical location	
Hand/wrist/elbow/shoulder	16/7/2/1, 26 (45.6%)
Foot/knee/hip	18/2/5, 25 (43.9%)
Lung	5 (8.8%)
Supraglottic area of larynx	1 (1.8%)
Histologic location	
Soft tissue adjacent to the joints	36 (63.2%)
Subcutis	9 (15.8%)
Dermis	6 (10.5%)
Lung parenchyma	5 (8.8%)
Submucosal layer of supraglottic area	1 (1.8%)

*Biologics: infliximab (TNFi biologic), abatacept (non-TNFi biologics); † Other immunosuppressive drugs: bucillamine, tacrolimus, mizoribine; *NSAIDs*, non-steroidal anti-inflammatory drugs; *DMARDs*, disease-modifying anti-rheumatic drugs; *ACR*, American College of Rheumatology; *RF*, rheumatoid factor; *ACPA*, anti-citrullinated protein antibodies; *ULN*, upper limit of normal; *anti-TG*, anti-thyroglobulin; *anti-TPO*, anti-thyroid peroxidase; *ANA*, anti-nuclear antibodies; *ANCA*, anti-neutrophil cytoplasmic antibody; *TNFi*, tumor necrosis factor inhibitors

cytoplasmic antibody (ANCA, 2 cases), anti-thyroid peroxidase (TPO, 1 case), anti-nuclear antibodies (ANA, 1 case), anti-Scl-70 (1 case), and anti-SS-B/La (1 case). Furthermore, three patients tested positive for two autoimmune markers (anti-TG and anti-TPO, cryoglobulins and anti-SS-A/Ro, cryoglobulins and anti-SS-B/La, respectively; Table 1 and supplemental material 1).

Fifty-six patients (98.2%) received treatment by at least one type of disease-modifying anti-rheumatic drugs (DMARDs) such as hydroxychloroquine (HCQ), leflunomide (LEF),

methotrexate (MTX), and sulfasalazine (SSZ). Among them, 44 (77.2%) patients received a combination of oral steroid and DMARDs treatment. One patient was treated with mizoribine, not DMARDs. Six patients were also administered with additional biologics (3 patients, 2 used abatacept, and 1 used infliximab) and other immunosuppressive drugs (3 patients, 2 used bucillamine, and 1 used tacrolimus). In addition, fifty-two (91.2%) patients were administered non-steroidal anti-inflammatory drugs (NSAID) for pain control (Table 1 and supplemental material 1).

The common sites of rheumatoid nodules were soft tissues adjacent various joints (36 cases, 63.2%), subcutis (9 cases, 15.8%), dermis (6 cases, 10.5%) of hand (16 cases, 28.1%), wrist (7 cases, 12.3%), elbow (2 cases, 3.5%), shoulder (1 case, 1.8%), foot (18 cases, 31.6%), knee (2 cases, 3.5%), and hip (5 cases, 8.8%). Rheumatoid nodules were also found in lung parenchyma (5 cases, 8.8%) and the submucosal layer of supraglottic area (1 case, 1.8%). Detailed data was described in Table 1 and supplemental material 1.

Among all patients, 35 (61.4%), 15 (26.3%), and 3 patients underwent surgical excision, due to complications of RA (uncontrolled pain or deformity; diagnosis of rheumatoid nodule histologically made at this time), the possibility of neoplastic disease, and the possibility of benign cystic lesion, respectively. One patient underwent wedge resection of the lung for suspected tuberculosis; another underwent excisional biopsy for suspected infectious bursitis in the hip; remaining two were also suspected of calcinosis cutis and panniculitis (Table 2).

Histopathological features

In all cases, eosinophilic necrobiosis was present in at least one focus area (Fig. 1a). Most of them were chronic with stromal fibrosis (55 cases, 96.5%), and in some cases accompanied by dystrophic calcification (5 cases, 8.8%) and cholesterol cleft (1 case, 1.8%). The palisading epithelioid or elongated histiocytes were apparently seen in 47 (82.5%) cases. Lymphocytic infiltration around the small blood vessels (39 cases, 68.4%) and cystic degeneration (36 cases, 63.2%) were also observed. In 33 (57.9%) cases, necrobiosis contained neutrophils and nuclear debris, which were widespread in cases where rheumatoid nodules occurred in the lungs (Fig. 1b). All rheumatoid nodules of the lungs were histologically located in the parenchyma, adjacent to the pleura. No definite vasculitis was seen in all cases (Table 3).

In five cases, eosinophilic amorphous materials were scattered into granulation tissues and surrounding stromal tissues (Fig. 1c). Cystic degeneration and associated multinucleated giant cells were also observed. In these cases, neutrophil infiltration was rarely observed and tended to show many foamy histiocytes (Fig. 1d).

Lendrum staining was performed in 18 cases for fibrin identification; 16 (88.9%) cases showed focal positivity in necrobiosis (Fig. 2a), whereas, 2 cases were negative. Alcian blue staining was performed in 10 cases, and all 10 cases tested positive. Among them, 5 cases tested positive in necrobiosis and surrounding stromal tissue, and the other 5 cases tested positive in only stromal tissues around necrobiosis (Fig. 2b).

We also analyzed the association between histopathological features with clinical characteristics, clinical impression, and imaging assessment. The palisading epithelioid or elongated histiocytes were significantly associated with regarding as RA rather than other diseases in imaging assessment ($P = 0.010$), and bone erosion was more frequently observed in cases with cleft or cystic degeneration ($P = 0.051$). The detailed data was presented in Supplementary Table 1–4.

Discussion

In this study, we reviewed the clinical, imaging, and histologic features of 57 patients diagnosed with rheumatoid nodule.

Table 2 Clinical impression and imaging assessment of the 57 rheumatoid nodules

Clinical impression	**Case no. (%)**
Rheumatoid arthritis (with/without rheumatoid nodules)	35 (61.4%)
Neoplastic conditions	15 (26.3%)
Infectious conditions	2 (3.5%)
Benign cystic lesion	3 (5.3%)
Others	2 (3.5%)
Imaging assessment	**Case no. (%)**
Rheumatoid arthritis (with/without soft tissue swelling)	43 (75.4%)
Neoplastic conditions	4 (7.0%)
Infectious conditions	4 (7.0%)
Benign cystic lesion	1 (1.8%)
Others	4 (7.0%)
Not available	1 (1.8%)

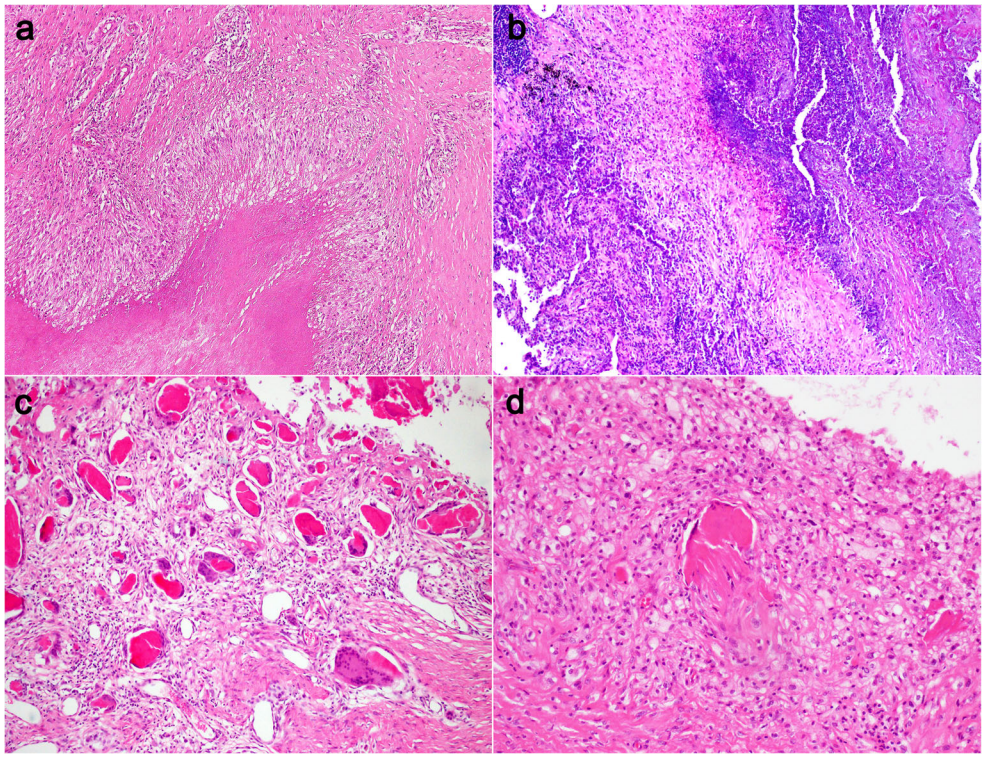

Fig. 1 Histopathologic features of rheumatoid nodules. The central eosinophilic necrobiosis and palisading elongated histiocytes are typical histologic features. In the surrounding tissues, lymphocytic infiltration around small blood vessels and stromal fibrosis are observed (**a**, H&E stain, × 100). Neutrophil infiltration and nuclear debris were more prominent in rheumatoid lung nodules (**b**, H&E stain, × 100). In some cases, eosinophilic amorphous material was scattered into granulation tissue. Multinucleated giant cells were also observed (**c**, H&E stain, × 200). It is mainly composed of foamy histiocytes rather than epithelioid or elongated histiocytes in the few cases (**d**, H&E stain, × 200)

Rheumatoid nodules are generally associated with high disease activity and poor prognosis of RA [1, 12]; in most cases, surgical removal is not necessarily required. Therefore, the number of cases of histologically confirmed rheumatoid nodules is small. The study included 57 patients who had undergone surgical excision for complications of RA or underwent biopsy or excision for differential diagnosis.

Most of the patients were female, with elevated RF and ACPA scores in most (98.2%) of the patients with rheumatoid nodule, as observed in previous studies [12, 13]. Only one patient did not have elevated RF and ACPA. Also, 14 patients tested positive for various serum autoimmune markers. Anti-TG and anti-TPO tests were performed to differentiate Hashimoto thyroiditis from patients suspected of hypothyroidism. Anti-SS-A/Ro and anti-SS-B/La tests were performed to differentiate secondary Sjögren's syndrome due to RA. Two patients were clinically suspected of systemic sclerosis and associated interstitial lung disease, and only one patient was anti-Scl-70 positive.

Table 3 Histopathological features of the 57 rheumatoid nodules

Histopathological features	Case no. (%)
Eosinophilic necrobiosis	57 (100%)
Stromal fibrosis	55 (96.5%)
Palisading epithelioid or elongated histiocytes	47 (82.5%)
Perivascular lymphocytic infiltrate	39 (68.4%)
Cleft or cystic degeneration	36 (63.2%)
Neutrophils with nuclear debris	33 (57.9%)
Definitive vasculitis	0 (0%)

MTX and LEF are known to be related to accelerate rheumatoid nodule development. In the present study, 53 (93.0%) patients received MTX and/or LEF treatment. The mechanism of action is yet to be clearly identified, but recent studies on rheumatoid nodule patients treated with MTX suggest that specific genotypes and changes in the expression of some genes may have affected nodule development [14, 15]. Pathogenic mechanisms of rheumatoid nodules are unclear. In previous studies, both rheumatoid nodules and rheumatoid synovial membranes expressed pro-inflammatory cytokines (TNF-α, IL-1β, etc.) and anti-inflammatory cytokines (IL-1Ra, TGF-β, etc.) [2, 4, 16]. On the other hand, the expression pattern of IL-17 families suggests a difference between a rheumatoid nodule and synovial inflammatory response [4].

Sites of rheumatoid nodules varied, but the soft tissues around the joints were the most frequently affected. There were 5 cases of rheumatoid nodules diagnosed in the lungs, all of which were adjacent to the pleura. Rheumatoid nodules are known to occur predominantly in the peripheral or

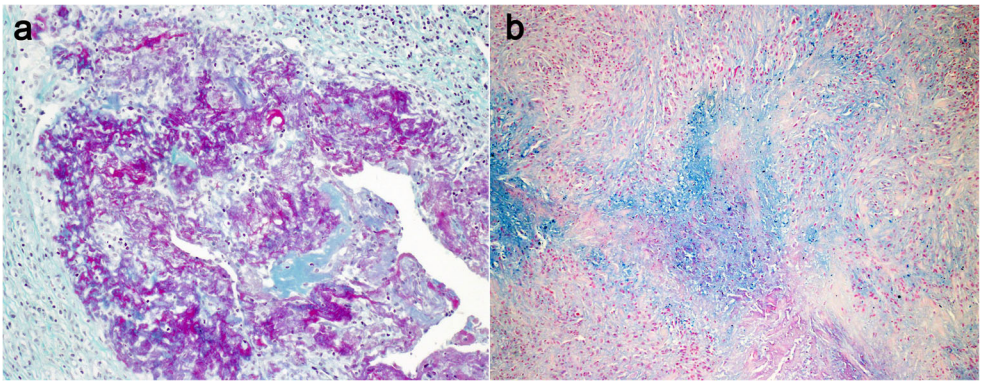

Fig. 2 Special staining results of rheumatoid nodules. In some cases, Lendrum fibrin staining showed diffuse positivity in necrosis (**a**, Lendrum fibrin stain, × 200). Alcian blue staining showed various staining patterns and positivity in necrosis and surrounding stroma in this case (**b**, Alcian blue stain, × 100)

subpleural layer of the lungs and seem to be consistent with our study [17].

Although the median duration between onset of treatment for RA and occurrence of rheumatoid nodule was 12 years, the duration was shorter in 4 cases (about 1 year). Except for one case involving the wrist, three cases were suspected tumorous conditions. In these cases, nodules were located in the ischial area of hip, larynx, and lung. In one case, rheumatoid nodule was diagnosed before the diagnosis of RA. The nodule was located in the 3rd intermetatarsal space of the foot. The nodule was initially suspected to be a Morton neuroma clinically but was diagnosed as a rheumatoid nodule histologically after resection. Histologically, typical forms of rheumatoid nodules were identified, and thickened nerve bundles and fibrosis surrounding them were observed. It is known that rheumatoid synovitis and rheumatoid nodule mimic Morton neuroma in RA patients [18]. Therefore, rheumatoid nodules should be considered in the differential diagnosis of Morton's neuroma in not only RA patients but also in asymptomatic patients who have never been tested for rheumatoid antibodies.

RA is an important factor in increasing the risk of cardiovascular disease (CVD), along with traditional risk factors [19, 20]. The specific risk factors that increase CVD risk in patients with RA have been studied, and several risk assessment methods have been suggested to evaluate the precise CVD risk [21]. The presence of extra-articular manifestation is known to be an important factor in raising CVD risk in RA patients [22, 23]. Thus, although it is not clear whether rheumatoid nodules are an independent risk factor, identification of rheumatoid nodules in RA patients may be important for risk assessment and for proper management.

In all cases, several or single central necrobiosis was observed. The necrobiosis included fibrinoid material, consisting of altered collagen, ground substance, and deposited extrinsic material such as fibrin [2], which was confirmed by Lendrum staining. Also, alcian blue staining was positive, suggesting that mucosubstances may be present in necrobiosis. The palisading epithelioid or elongated histiocytes surrounding the necrobiosis were not clearly identified in some cases, and these cases showed necrobiosis surrounded by granulation tissues with some histiocytes. Infiltration of lymphocytes and neutrophils around the small vessels of the peripheral area was observed in several cases; however, definite vasculitis was not observed. Neutrophil infiltration and nuclear debris were more prominent in rheumatoid nodules of lung parenchyma, and these features might make it difficult to distinguish rheumatoid nodules from infectious diseases such as mycobacterial or fungal infection.

One case, which was excluded from the study, was histologically compatible with rheumatoid nodule showing necrobiosis with palisading histiocytes. The patient was a 6-year-old girl who had a mass in the right arm. She did not have arthralgia and evidence of RA in the laboratory test (negative RF and ACPA). And this case was not clinically relevant to the diagnosis of RA and RA did not occur during the follow-up period after biopsy. It seems to correspond to cases referred to as benign rheumatoid nodules of childhood in previous literature. Histologic findings of these cases are known to be no different from rheumatoid nodules in patients with RA [24, 25].

There are several limitations of this study. It is a retrospective study and may be missing content because it relies on electronic medical records. In particular, it was difficult to determine the time when rheumatoid nodules occurred, and there were cases that were not clinically expected. And the patients included in the study were too small to represent all RA patients. Also, in most cases, patients underwent medical treatment for RA before diagnosis of rheumatoid nodule, and the changes in histologic findings could not be considered.

In conclusion, the rheumatoid nodule is a characteristic lesion in patients with RA, and thus, differentiation from neoplastic or infectious diseases is important for choosing a treatment method. Clinicopathological review of rheumatoid nodule could help clinicians understand the pathophysiology and

make accurate diagnosis of rheumatoid nodules. It will be necessary to identify these characteristics in relation to the pathogenesis of rheumatoid nodules through further studies.

Author contributions Seong Sik Bang: assessment of the special staining slides; review of histological material; data analysis; drafting of the manuscript; preparation of the illustrations; preparation of the final text

Yeseul Kim: assessment of the immunohistochemical slides; review of histological material; preparation of the final text

Kiseok Jang: provided clinical data; preparation of the final text

Seung Sam Paik: provided clinical data; preparation of the final text

Su-Jin Shin: elaboration of the research concept; review of histological material; choice of cases for the study; general supervision of the study; drafting of the manuscript and preparation of the final text

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Compliance with ethical standards

The Institutional Review Board of the Hanyang University Hospital (HYUH 2018-10-006) approved the study and waived the requirement for informed consent.

Disclosures None.

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