Case Report

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Unusual Manifestation of Immunoglobulin G4-Related Disease Involving the Upper Arm: A Case Report

상완에 발생한 면역글로불린 G4 연관 질환의 비전형적 발현: 증례 보고

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Immunoglobulin G4 (IgG4)-related disease is a rare systemic fibroinflammatory condition characterized by organomegaly or tumefactive lesions associated with lymphoplasmacytic infiltration rich in IgG4 plasma cells. We report a case of IgG4-related disease involving the subcutaneous layer of the left upper arm in a 48-year-old female presenting with an unusual soft tissue mass. US and MRI showed an irregular infiltrative soft tissue mass, indicating possible malignancy or inflammation. We discuss the diagnostic criteria, histopathologic features, radiological features, and treatment of IgG4-related disease.

Index terms IgG4-Related Disease; Magnetic Resonance Imaging; Ultrasonography

INTRODUCTION

Immunoglobulin G4-related disease (IgG4-RD) is a rare multiorgan condition characterized by the infiltration of IgG4-positive plasma cells and lymphocytes with associated fibrosis in one or more organs or organ systems (1). Various organs may be either simultaneously or consecutively involved, and the most commonly affected organ is the pancreas (1). Here, we report a case of a patient with IgG4-RD with an unusual presentation of a soft tissue mass in the subcutaneous layer of the left upper limb, which is extremely rare.

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CASE REPORT

In May 2019, a 48-year-old female was referred to the orthopedic department unit of our hospital with an incidentally found palpable mass 3 weeks prior in the left upper arm without pain or tenderness. The patient had a history of iron deficiency anemia. Laboratory results revealed hemoglobin of 10.3 g/dL (normal 12.0–16.0 g/dL), white blood cells of 4060/μL (normal 4000–10000/μL), and C-reactive protein of 0.3 mg/dL (normal ≤ 0.3 mg/dL).

Radiologic studies, including US and MRI, were performed. On MRI, T2-weighted images showed a 1.3 cm × 1.2 cm × 1.6 cm heterogeneous and slightly hyperintense mass-like lesion with an infiltrative margin in the subcutaneous layer of the left upper arm. Internal focal areas of hypointensity indicate fibrotic components within the tumor. The lesion showed isointensity to slight hyperintensity on T1-weighted images and heterogeneous enhancement on contrast-enhanced fat-suppressed T1-weighted images. Adjacent thick enhancing fascia extending from the mass as a tail-like margin and adjacent thick enhancing skin suggested that there might be an infiltrative spread of the tumor or inflammatory cells along the fascial plane and the skin (Fig. 1A). On ultrasonography, the mass-like lesion showed a heterogeneous internal echotexture with an ill-defined margin and a hyperechoic halo in the subcutaneous layer of the left upper arm. Doppler ultrasonography showed internal vascularity of the lesion (Fig. 1B). On the basis of imaging features, the patient underwent an US-guided biopsy of the mass to exclude malignancy.

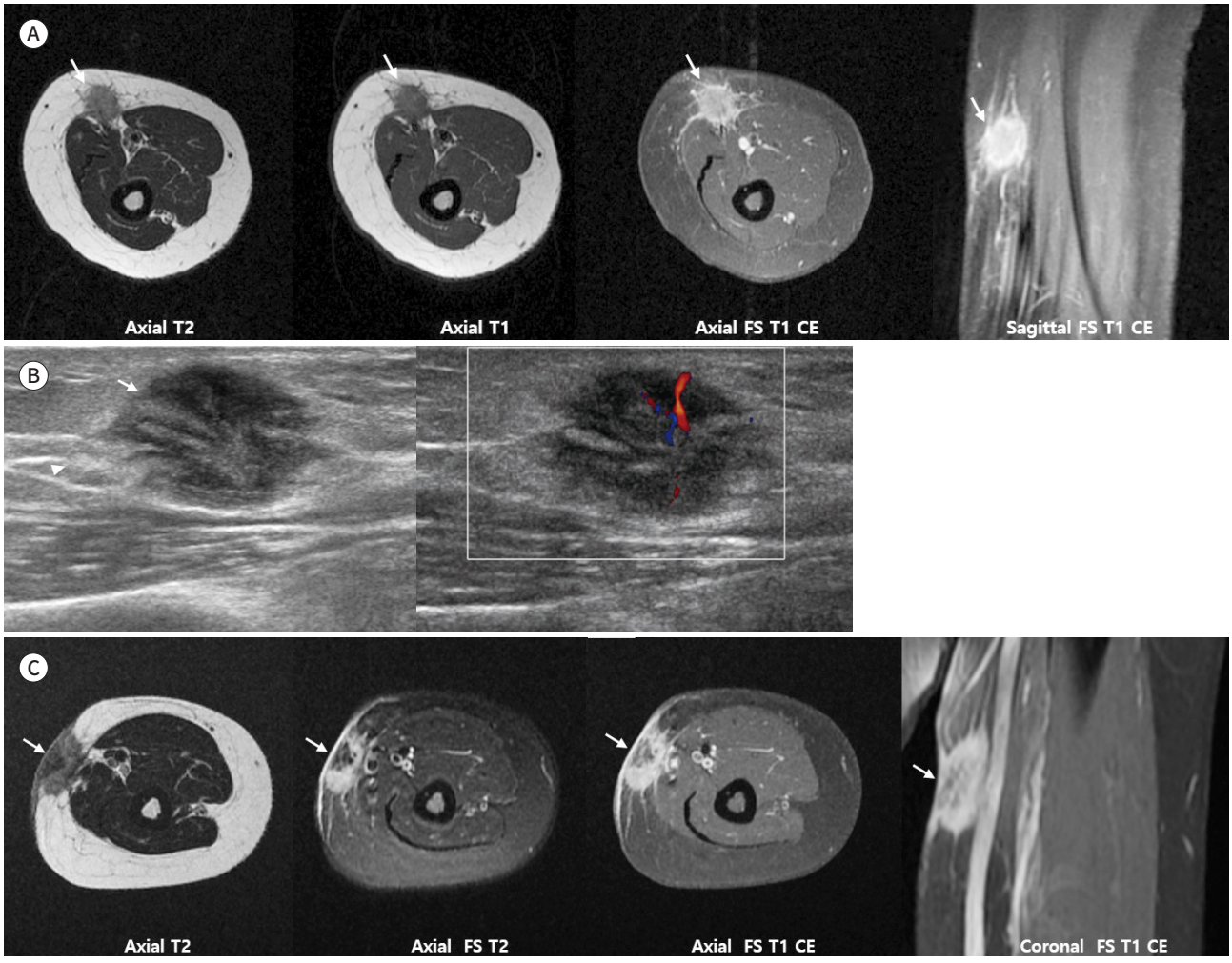
Histological analysis revealed chronic active inflammation with focal necrosis and extensive plasma cell infiltration, favoring reactive changes rather than plasmacytoma. In addition, Kappa-in situ hybridization (ISH) and Lambda-ISH were positive, which are positive in plasma cells with a polyclonal pattern. Clinicians and radiologists didn't suspect IgG4-RD and perform immunostaining for IgG4.

The patient was not able to undergo steroid treatment, but revisited the hospital 18 months after the time of biopsy due to the increased size of the palpable mass and changed color of the overlying skin. Laboratory results revealed hemoglobin of 13.8 g/dL (normal 12.0–16.0 g/dL), white blood cells of 3990/μL (normal 4000–10000/μL), and C-reactive protein of 0.02 mg/dL (normal ≤ 0.3 mg/dL).

The patient underwent MRI. The mass-like lesion was enlarged from 1.3 cm × 1.2 cm × 1.6 cm to 1.9 cm × 1.3 cm × 2.9 cm. T2-weighted images showed a more heterogeneous lesion with an increased extent of focal area hypointensity, indicating a fibrotic component within the tumor. Contrast-enhanced fat-suppressed T1-weighted images showed more heterogeneous enhancement. In addition, the margin of the mass became more infiltrative, and the adjacent thick enhancing fascia and skin became more prominent (Fig. 1C).

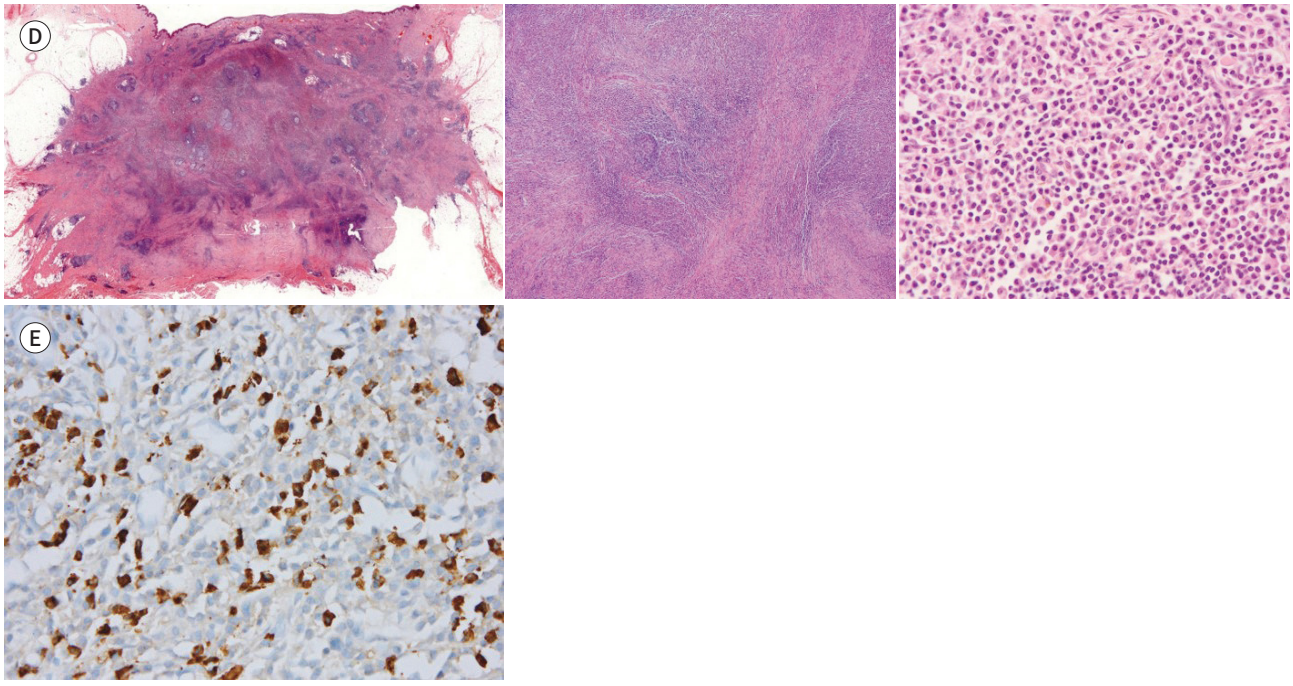
Tumor excision was performed due to the inconclusive result of the previous US-guided biopsy. Histological analysis revealed dense inflammatory infiltrates separated by fibrotic bands. The inflammatory cells consisted of plasma cells and some lymphocytes. In addition the histological analysis correlated with MR imaging findings. The lesion's center, which showed hypointensity on T2-weighted images, had higher cellularity and vascularity, whereas the periphery, which showed hyperintnsity on T2-weighted images, had lower cellularity and vascularity. The lesion's outermost portion was infiltrating pseudocapsule-like fibrous

Fig. 1. IgG4-related disease involving the subcutaneous layer of the left upper arm in a 48-year-old female.
A. Axial T2-weighted images show a 1.3 cm × 1.2 cm × 1.6 cm heterogeneous and slightly hyperintense mass-like lesion (arrows) with an infiltrative margin in the subcutaneous layer of the left upper arm. Internal focal areas of hypointensity indicate fibrotic components within the tumor. The lesion shows isointensity to slight hyperintensity on axial T1-weighted images and heterogeneous enhancement on axial and sagittal CE FS T1-weighted images. Adjacent thick enhancing fascia extending from the mass and adjacent thick enhancing skin suggest an infiltrative spread of the tumor or inflammatory cells along the fascial plane and the skin.
B. On ultrasonography, the mass-like lesion (arrow) shows a heterogeneous internal echotexture with an ill-defined margin and a hyperechoic halo (arrowhead) in the subcutaneous layer. Doppler ultrasonography shows internal vascularity of the lesion.
C. After 18 months, the mass-like lesion (arrows) increased in size to 1.9 cm × 1.3 cm × 2.9 cm. Axial T2-weighted and FS T2-weighted images show more heterogeneous lesions with an increased extent of focal area of hypointensity, indicating a fibrotic component within the tumor. Tumor periphery shows hyperintensity. Axial and coronal CE FS T1-weighted images show more heterogeneous enhancement. In addition, the margin of the mass became more infiltrative, and the adjacent thick enhancing fascia and skin became more prominent.
CE = contrast-enhanced, FS = fat-suppressed, IgG4 = immunoglobulin G4



tissue (Fig. 1D). Immunostaining for IgG4 (× 400) showed increased IgG4-positive cells (150–200 cells/high-power field [HPF]) and an increased IgG4/IgG ratio (30%–40%) (Fig. 1E). Laboratory results revealed a serum IgG subclass 4 of 2220 mg/L (normal 30–3010 mg/L). The patient met the diagnostic criteria of IgG4-RD. Subsequent computed tomography of the abdominopelvic cavity, chest, and head and neck did not demonstrate other sites of IgG4-RD. After that, the patient was placed on outpatient follow-up without steroid or immunosuppressant agent treatment.

Fig. 1. IgG4-related disease involving the subcutaneous layer of the left upper arm in a 48-year-old female. (Continued)
D. In the scan view, the lesion's center, which shows hypointensity on T2-weighted images, has higher cellularity and vascularity, whereas the periphery, which showeshyperintensity on T2-weighted images, has lower cellularity and vascularity. The lesion's outermost portion is shown infiltrating pseudocapsule-like fibrous tissue (H&E stain, × 4.3). In the low-power view (middle box), the lesion shows dense inflammatory infiltrates separated by fibrotic bands (H&E stain, × 40). In the high-power view (right box), inflammatory cells consists of plasma cells and some lymphocytes (H&E stain, × 400).
E. Immunostaining for IgG4 shows increased IgG4-positive cells (150–200 cells/high-power field) and an increased IgG4/IgG ratio (30%–40%) (× 400).
H&E = hematoxylin and eosin, IgG4 = immunoglobulin G4



This study was approved by the Institutional Review Board of Inje University Busan Paik Hospital (IRB No. 2021-12-082).

DISCUSSION

IgG4-RD was first recognized as a distinct disease in 2003 (1). IgG4-RD is an immune-mediated fibroinflammatory condition that can affect various organs either simultaneously or consecutively (1). There are strong predispositions for certain organs, including the pancreas, biliary tree, major salivary glands, lacrimal glands, kidneys, and retroperitoneum (1). The clinical symptoms of IgG4-RD depend on the affected organs and are generally mild, with no fever or C-reactive protein level elevation (1, 2). Its epidemiology is not well known, and the prevalence rates of IgG4-RD are underestimated (1, 2). IgG4-RD typically affects middle- to elderly aged men, with an onset at 50–70 years (1, 2). To our knowledge, this is the first case of a patient with IgG4-RD presenting as a soft tissue mass in the subcutaneous layer, describing radiologic features on US and MRI (Table 1) (3-6).

A Japanese group proposed comprehensive diagnostic criteria for IgG4-RD (7). 1) clinical study shows characteristic diffuse/localized swelling or masses in single or multiple organs, 2) hematological study shows elevated levels of serum IgG4 (≥ 135 mg/dL), and 3) histopath-

Table 1. Soft Tissue Involvement of Immunoglobulin G4-Related Disease

Reference	Sex	Age	Site	Treatment
Martínez et al., 2013 (3)	Male	32	Skeletal muscle of left forearm	Steroid
Cheung et al., 2015 (4)	Male	40	Skeletal muscle of right thigh	Excision
Khan et al., 2016 (5)	Female	68	Skeletal muscle of left hip	Steroid
Creze et al., 2020 (6)	Male	16	Left femoral triangle	Excision
Current study, 2022	Female	80	Subcutaneous layer of left forearm	Excision

ological study shows marked lymphocyte and plasmacyte infiltration and fibrosis, as well as IgG4-positive plasma cell infiltration (ratio of IgG4-/IgG-positive cells > 40%, and IgG4-positive plasma cells/HPF > 10) (7). The diagnosis of IgG4-RD is considered definite if all three criteria are met, probable if the first and third criteria are met, and possible if the first and second criteria are met (7). However, as shown in our case, IgG4-RD can be underdiagnosed due to a lack of recognition of this condition and a lack of utilization of a specific immunohistochemical approach (7).

Common imaging features of IgG4-RD are organomegaly and/or a tumefactive appearance with inflammatory and fibrotic components (8). It usually involves multiple organs (8). Subcutaneous layer involvement of IgG4-RD may manifest as a soft tissue mass, as in our patient (4, 6). Ultrasonography findings may demonstrate a variable pattern of echogenicity with ill-defined margins. CT findings may demonstrate soft tissue lesions with infiltrative margins (4, 6). Enhancement patterns vary, possibly due to varying degrees of fibrosis and cellular infiltration (4, 6). MRI findings may demonstrate various signal intensity patterns on T2-weighted images with progressive enhancement, possibly due to fibrotic components (4, 6). In addition, inflammatory cells may infiltrate adjacent anatomic structures, such as fascia and skin, which may appear as thickening of the fascia and skin with enhancement (4, 6). It is difficult to differentiate from malignant tumors and other fibroinflammatory diseases by imaging features alone (4, 6, 8). Therefore, histopathology and immunostaining are necessary for differentiating among these conditions (4, 6, 8).

In our patient, the radiologic studies showed an infiltrating soft tissue mass of the subcutaneous layer with linear fascial extension (fascial tail sign) and internal fibrotic components. Our initial differential diagnoses included both benign and malignant lesions, such as nodular fasciitis, fibromatosis, myxofibrosarcoma and undifferentiated pleomorphic sarcoma (9, 10). Nodular fasciitis and fibromatosis may demonstrate variable signal intensity on T1- and T2-weighted images depending on the histologic composition (9, 10). After the administration of contrast material, nodular fasciitis may demonstrate diffuse enhancement, and fibromatosis may demonstrate marked enhancement (9, 10). Sarcomas may demonstrate heterogeneous signal intensity on T1- and T2-weighted images and heterogeneous enhancement owing to areas of collagen, myxoid components, necrosis and hemorrhage (9, 10).

Most clinical manifestations of IgG4-RD respond to steroids and immunosuppressants (2). Steroids are the first-line treatment. Immunosuppressants are used in patients who do not respond to steroids (2). Relapses are common with the discontinuation of therapy (2). Whether IgG4-RD patients should receive maintenance therapy to prevent disease relapse is under debate (2).

In summary, we present a case of a patient with IgG4-RD with an unusual presentation of a soft tissue mass in the subcutaneous layer of the left upper limb, mimicking a malignant tumor or fibroinflammatory conditions. When an infiltrative mass in the subcutaneous layer with internal fibrotic components invades the normal anatomic barriers, a tumefactive manifestation of IgG4-RD should be considered as a differential diagnosis. It can be managed conservatively with corticosteroids, and unnecessary aggressive surgical interventions can be prevented.

Author Contributions

Conceptualization, L.S.J.; data curation, all authors; formal analysis, C.H.J.; methodology, P.J.H.; resources, all authors; supervision, L.S.J.; visualization, P.J.H., C.H.J.; writing—original draft, P.J.H.; and writing—review & editing, L.S.J.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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상완에 발생한 면역글로불린 G4 연관 질환의 비전형적 발현: 증례 보고

박진희 · 이선주* · 추혜정

면역글로불린 G4(immunoglobulin G4; 이하 IgG4) 관련 질환은 드문 전신성 섬유염증 상태로 IgG4 형질 세포가 풍부한 림프구 침윤과 관련된 기관 비대 또는 종창성 병변을 특징으로 한다. 우리는 48세 여자 환자에서 드문 소견인 연조직 종괴로 발현된 왼팔의 피하층을 침범한 IgG4 관련 질환 증례를 보고하고자 한다. 초음파 및 자기공명영상을 촬영하였으며 악성 또는 염증 병변이 의심되는 불규칙하며 침윤성 경계를 갖는 연조직 종괴가 관찰되었다. 우리는 IgG4 관련 질환의 진단 기준, 조직 병리학적 특징, 영상의학적 특징, 및 치료 방법에 대해 논의하고자 한다.

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