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Erdheim-Chester disease with cardiac involvement: a new case report

Kalp tutulumlu Erdheim-Chester hastalığı: Yeni bir olgu sunumu

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Erdheim-Chester disease (ECD) is a rare, non-Langerhans cell histiocytosis of unknown etiology, characterized by multiple organ involvement. Erdheim-Chester disease is usually diagnosed on the basis of characteristic radiologic and histopathological findings. Lesions may be skeletal or extraskeletal and may involve the skin, lung, heart, and central nervous system. In this article, we report a 62-year-old male case admitted with the complaints of cough and dyspnea. Imaging studies showed multiple osteosclerotic lesions of the bones, a large amount of pericardial effusion, and a mass which surrounds the right atrium. Cytological examination of the pericardial effusion material revealed foamy histiocytes with multinuclear giant cells. Pericardium and internal mammary artery biopsies showed fibrosis with infiltrating foamy histiocytes which were MAC38(+) and S100, CD1a(–) immunohistochemically. Based on these findings, the patient was diagnosed as ECD with extraskeletal manifestations and treated with systemic corticosteroids and chemotherapy (cyclophosphamide).

Key words: Erdheim-chester disease; non-Langerhans cell histiocytosis; osteosclerosis; pericardial effusion.

Erdheim-Chester hastalığı (ECD); nadir, etyolojisi bilinmeyen, non-Langerhans hücreli histiyositöz sınıfından çoklu organ tutulumu ile karakterize bir hastalıktır. Erdheim-Chester hastalığına genellikle karakteristik radyolojik ve histopatolojik bulgulara göre tanı konulur. Lezyonlar iskelet sistemini etkileyebilir veya deri, akciğer, kalp ve santral sinir sistemi gibi iskelet dışı sistemleri tutabilir. Bu yazıda öksürük ve dispne yakınmaları ile başvuran 62 yaşında bir erkek hasta sunuldu. Görüntüleme incelemelerinde; kemiklerde yaygın osteosklerotik lezyonlar, geniş miktarda perikardiyal efüzyon ve sağ atriyumu çevreleyen kitle olduğu tespit edildi. Perikardiyal efüzyon materyalinden yapılan sitolojik incelemede multinükleer dev hücreler ile köpüksü histiyositler görüldü. Perikard ve internal meme arteri biyopsilerinde, immünohistokimyasal olarak MAC38(+) ve S100, CD1a(–) olan köpüksü histiyositler ile çevreli fibrozis görüldü. Bu bulgulara dayanarak, hastaya iskelet dışı sistemlerin de tutulduğu ECD tanısı konuldu ve sistemik kortikosteroid ve kemoterapi (siklofosfamid) ile tedavi edildi.

Anahtar sözcükler: Erdheim-chester hastalığı; non-Langerhans hücreli histiyositoz; osteoskleroz; perikardiyal efüzyon.

Erdheim-Chester disease (ECD) is a rare, non-inherited, non-Langerhans form of histiocytosis. The disease was first described in 1930 by William Chester as "lipoid granulomatosis" and has gone by various other names including histiocytosis X.[1,2] Finally, it was named ECD after the pathologist Erdheim with whom Chester worked.[3] Erdheim-Chester disease is a local or systemic infiltrative disorder. There are no definitive diagnostic criteria for this entity, and diagnosis is usually based on radiological findings of osteosclerosis combined with histopathological evidence of foamy histiocytic infiltration.[4] This disease can affect multiple organs and shows various clinical manifestations depending on the organs that are involved. These range from

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asymptomatic disease to respiratory distress and/or cardiac failure.[5]

We describe here a patient simulating a cardiac tumor with pericardial effusion; however, in this case, the subject was suffering from ECD with cardiac involvement.

CASE REPORT

A 62-year-old man was referred to our hospital from another tertiary facility with a mass localized behind the right atrium and a large amount of pericardial effusion which had been ongoing for five months. Pericardiocentesis drained 700 cc of fluid, but one month later, pericardial effusion developed again. A cytological examination revealed that the pericardial fluid contained histiocytes and inflammatory cells, but no malignancy was seen in the cells. On physical examination, the blood pressure was 100/60 mmHg, the pulse rate was 58 beats per minute, and the patient's rhythm was sinus. He had no complaints of bone pain, but his effort was slightly decreased. He had a moderately elevated erythrocyte sedimentation rate (ESR), a moderately elevated C-reactive protein (CRP) level, and elevated serum IgG4 levels. A coronary angiogram showed that he had multiple coronary artery stenosis [70% in the left anterior descending (LAD) and 50% in the first diagonal]. His laboratory results showed an ESR of 26 mm/h and a CRP level of 5.02 mg/dL along with a leukocyte count of 17,500 cells per/L. Echocardiography revealed a 2.7 cm x 3.1 cm tumor behind the right atrium with mobile components toward the right atrium and 3 cm pericardial effusion. In addition, it disclosed that the mass surrounding the right coronary artery (RCA) (Figure 1). Furthermore, the echocardiography also showed mild tricuspid regurgitation and moderate mitral regurgitation. A radiographic investigation of the long bones determined that there was also diffuse sclerosis, and positron emission tomography (PET) with fluorine-18 flourodeoxyglucose (18F-FDG) revealed an increased uptake of 18F-FDG in the atrial tumor that surrounded the superior vena cava and infiltrated the RCA (Figure 2). The patient's operation plan was composed of coronary artery bypass graft (CABG) and excision of the mass. After the pericardiotomy, 1000 ml of fluid was drained, and the patient was not accepted as a suitable candidate for CABG due to the mass not being excisable because of the diffuse tumor-like infiltration of the pericardial tissue and extreme thickness of the myocardium, measuring approximately 1-1.5 cm in thickness around the right atrium and 0.5 cm in thickness over the coronary arteries. A biopsy of the pericardial mass was then taken, and it measured 1.5x1.5 cm in diameter. Afterwards, the pleuropericardial window was opened (Figure 3), and a biopsy of the internal mammary artery (IMA) was taken from a side branch. Next, percutaneous transluminal coronary angioplasty (PTCA) was performed, and an LAD coronary stent was implanted. The biopsy revealed foamy histiocytes nestled among granulomatous polymorphs, fibrosis, and xanthogranulomatosis, which is consistent with ECD. This diagnosis was confirmed both histologically and immunohistochemically. The infiltrating histiocytes contained intracytoplasmic lipids, and they tested positive for the monoclonal antibody MAC387 and negative for the CD1a and S100 proteins, thus highlighting their non-Langerhans histiocytic origin (Figure 4). Over the course of the four-week hospitalization, the patient's general condition returned to near normal, and his dyspnea, precordial pain, and edema were resolved. His treatment plan included 1000 mg of methylprednisolone, 500 mg of cyclophosphamide, and 400 mg mesna, which was to be given on the 7th, 10th, 15th, and 20th days of every month for one year, and oral prednisolone, which was initiated at 60 mg/day, but was to be progressively tapered after discharge.

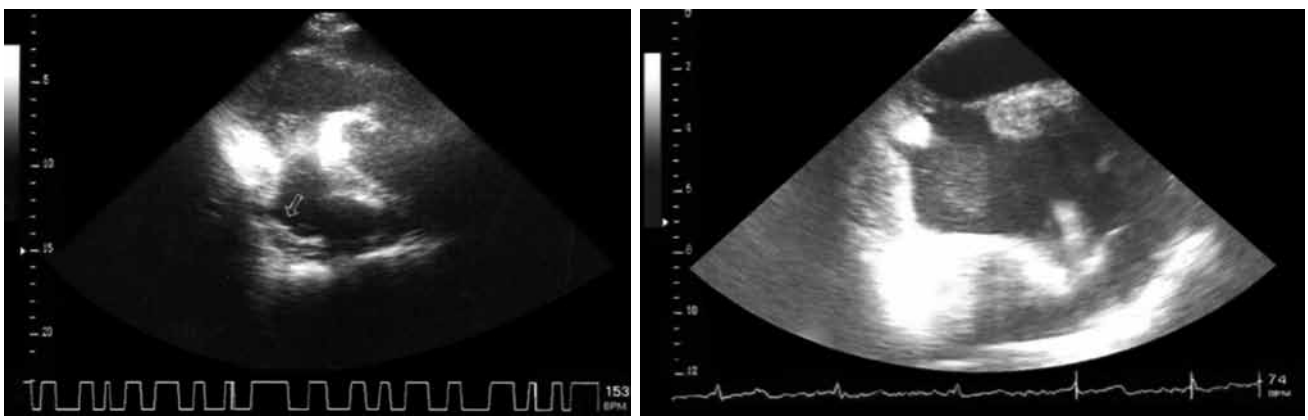
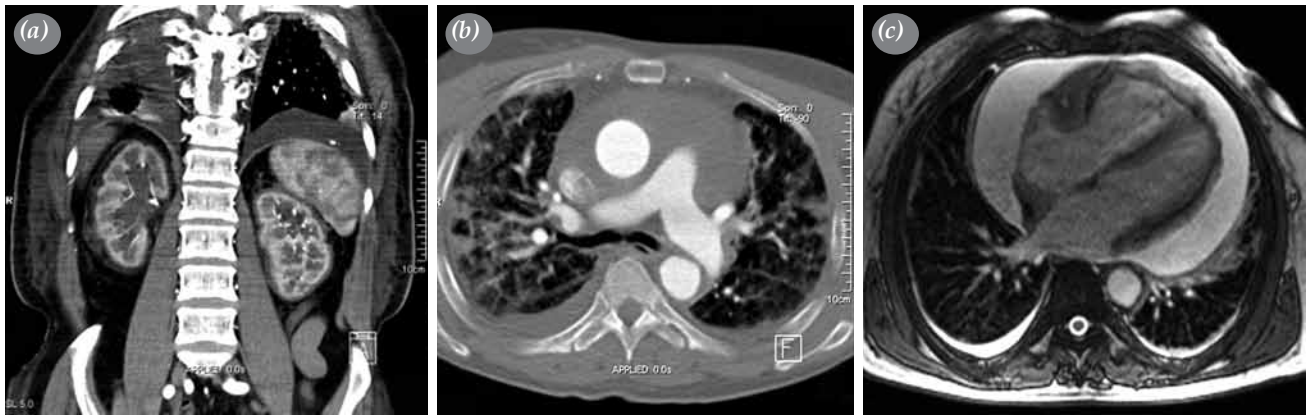


Figure 1. Transesophageal echocardiogram view of right atrial mass



Computed tomography images | Axial thorax computed tomography images | Axial postcontrast T_2 weighted images

Figure 2. (a) Coronal multiplanar reformation reconstruction increased density around kidney. **(b)** Interstitial thickening and focal increased of density in lung parenchyma. **(c)** Isointens mass surrounding right coronary artery mass reachs to superior vena cava pericardial and bilaterally pleural effusion.

The patient continues to do well with medical therapy and has had no further complaints related to his ECD.

DISCUSSION

Erdheim-Chester disease is a rare, non-Langerhans cell histiocytosis that is characterized by infiltrates of foamy histiocytes in conjunction with symmetric osteosclerotic changes in the long bones and the xanthomatous infiltration of tissues with foamy CD68+/CD1a- histiocytes. The etiology and pathogenesis of ECD remain unclear, although abnormal activation of monocytes may be involved.[6]

The clinical manifestations of ECD vary tremendously since the symptoms depend on the tissues that were infiltrated. A review of 59 ECD patients found that bone pain, predominantly involving the lower limbs, was the most frequent symptom (47% of patients), and that extraskeletal manifestations, including exophthalmos, diabetes insipidus (DI), and retroperitoneal histiocytic infiltration, were not uncommon (30% of patients).[4] Moreover, approximately half of patients with this disease had extraskeletal manifestations, for example exophthalmos, xanthelasma, interstitial lung disease, retroperitoneal "fibrosis" with perirenal or ureteral obstruction, renal failure, DI, and central nervous system and cardiovascular involvement.[7] In addition, 19% of ECD patients showed skin involvement, predominantly of the eyelids.[4]

Histopathological examinations are crucial for obtaining an accurate diagnosis, especially for differentiating ECD from other types of histiocytosis. The majority of infiltrating cells in ECD are foamy histiocytes, which are frequently associated with variable amounts of fibrosis and the presence of inflammatory cells such as lymphocytes, plasma cells, and Touton type giant cells.[8] Immunohistochemically, most histiocytes in ECD are negative for the S-100 protein and positive

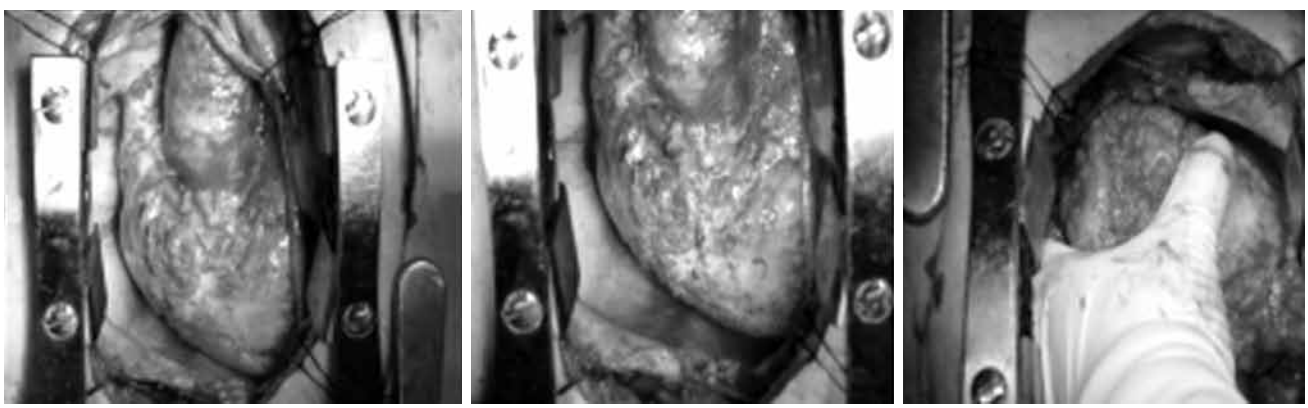


Figure 3. Surgical view of the mass towards right atrium and surrounds right coronary artery.

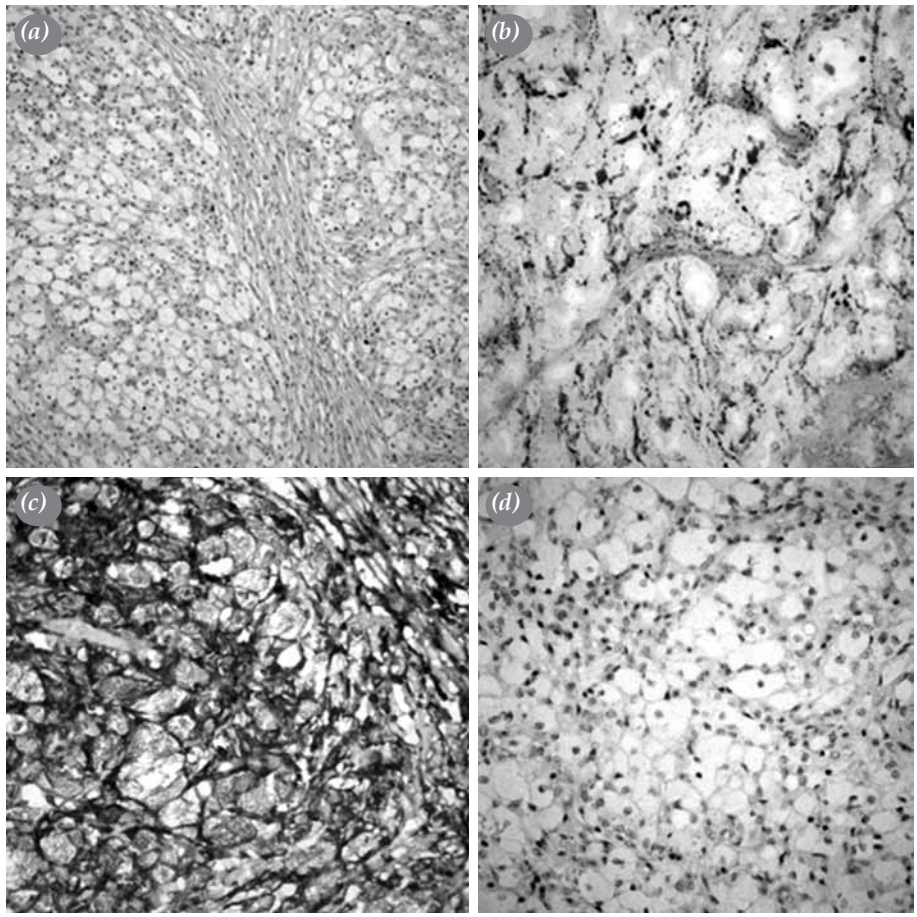


Figure 4. (a) The lesion is characterized by xanthomatous fibroinflammatory reaction. Numerous foamy cells accompanied by fibrosis and lymphoplasmacytic cell infiltration (H-E x 40). **(b)** Foamy cells contain fat droplets with fat stain (x 40). **(c, d)** Immunohistochemically foamy cells are positive with CD163 and negative for CD1a (x 40).

for the CD68 glycoprotein, indicating that these cells are from the macrophage lineage, not the dendritic cell lineage.

Apart from histological findings, the only specific signs of ECD are radiological findings in the long bones, such as symmetrical sclerosis of the metaphyses and diaphyses of the long tubular bones.[4] These features differentiate ECD from Langerhans cell histiocytosis in which the bone lesions are usually osteolytic and rarely involve the long bones.[9] In ECD, there is usually a sparing of the epiphyses and axial skeleton, although exceptions have been described.[10] The most commonly affected bones are the femur, tibia, and fibula, with the ulna, radius, and humerus being affected less often. In addition, mixed sclerotic and lytic lesions have been occasionally reported. In some patients with ECD, clinical bone symptoms can be mild or absent, as was the case in our study. Thus, bone scintigraphy may be useful for detecting bone lesions. Para-aortic and perirenal infiltration may lead to renal upper tract obstruction, which tends to be progressive. Ureteric stenting has been recommended until the active inflammation is resolved.[11] In addition, a nephrostomy can be difficult in view of the fibrous perinephric tissue seen in these patients.

The most common neurological presentations of ECD are DI, cerebellar syndromes, and orbital lesions.

Pulmonary involvement occurs in approximately 20% of cases, and chest radiographs showed diffuse interstitial infiltrates with upper zone predominance in three out of four patients in a series by Egan et al.[12]

Cardiovascular manifestations of ECD are underdiagnosed, as shown in an analysis by Haroche et al.,[13] in 2004 of the 178 cases known at that time.[14] They analyzed 72 patients with cardiovascular involvement and found that 54 (75%) of these had heart involvement.

Pericardial infiltration was found in 32 patients (44%) (leading to tamponade in five cases) and myocardial infarction (MI) was identified in 22 (31%). A right atrial tumor was discovered in six of these 22 patients, the same as in our case, and symptomatic valvular heart disease was noted in six others (3 aortic and 3 mitral regurgitations). Additionally, 19 patients (26%) had heart failure, leading to death in eight cases. Myocardial infarction was reported in six of these 19 cases and caused two more deaths. Forty of the 72 patients (56%) in the study by Haroche et al.[13] had a periaortic fibrosis, and 20 of these had a "coated aorta" aspect. Among the 58 patients (81%) who were available for follow-up, 35 (60%) died. Their deaths were due to cardiovascular involvement in 31% of the cases, confirming the severe prognosis of ECD with cardiovascular complications. The poor prognosis of ECD with cardiovascular involvement led us to systematically search for it. The frequency and pattern of cardiac involvement in ECD, which was unknown at the time of the study by Haroche et al.,[13] was detected by magnetic resonance imaging (MRI), a gated computed tomography (CT) scan of the heart, or both and was then presented. That series, which is the largest to date for ECD, illustrates the benefit of systematic screening for cardiac infiltration. One of the striking findings of ECD is the high frequency of right atrial and auriculoventricular sulcus involvement. Infiltration of the right heart has been classically described in angiosarcoma.[15] and lymphoma.[16] The pericardial thickening, which may lead to tamponade, the periarterial coronary infiltration and the "pseudoatrial" mass are notably seen very well on heart imaging. A systematic cardiac evaluation by MRI, CT scan, or both should be performed in ECD patients because these manifestations are not always clinically evident.

There are few reports of laboratory findings in patients with ECD, but they. usually have an increased ESR and a mildly increased alkaline phosphatase level.[17] In addition to an elevated ESR, our patient also had elevated levels of CRP and serum IgG4.

An optimal treatment for ECD has yet to be established, probably because of the rarity of the condition and the paucity of clinical trials. Systemic steroids, various cytotoxic agents, radiation therapy, and hematopoietic stem cell transplantation have all been used to treat patients with this condition, and these have had variable outcomes.[18,19] At present, interferon alpha is being used as the first-line treatment of ECD,[20] but its efficacy has been reported to be inconsistent or limited, especially for cardiovascular, cerebral, and mesenteric lesions.[7,20] Because of that, we preferred to not first use this biological therapy. In all patients, bone irradiation was transiently effective in the treatment of bone pain.

The prognosis of patients with ECD has been reported to be dismal, with a mean overall survival period of 32 months and a higher mortality rate than for patients with LCH (57% versus 30%).[4] The most commonly reported causes of death in patients with ECD include respiratory and heart failure, and involvement of the bones and soft tissues has been associated with the poor prognosis. Although ECD is a rare disease, approximately 350 such patients have been described to date. The true incidence of the disease may be much higher, and lack of knowledge of this condition along with difficulties in diagnosis may contribute to the apparent low incidence rate. We believe that increased awareness of ECD may enhance the prompt diagnosis and appropriate management of this disease.

Declaration of conflicting interests

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REFERENCES

1. Jaffe HL. Lipid (cholesterol) granulomatosis. In: Jaffe HL, editor. Metabolic, degenerative, and inflammatory diseases of bones and joints. Philadelphia: Lea & Febiger; 1972. p. 535-41.
2. Chester W. Uber lipoidgranulomatose. Virchow Arch (Pathol Anat) 1930;279:561-602.
3. Egan AJ, Boardman LA, Tazelaar HD, Swensen SJ, Jett JR, Yousem SA, et al. Erdheim-Chester disease: clinical, radiologic, and histopathologic findings in five patients with interstitial lung disease. Am J Surg Pathol 1999;23:17-26.
4. Veyssier-Belot C, Cacoub P, Caparros-Lefebvre D, Wechsler J, Brun B, Remy M, et al. Erdheim-Chester disease. Clinical and radiologic characteristics of 59 cases. Medicine (Baltimore) 1996;75:157-69.
5. Sheu SY, Wenzel RR, Kersting C, Merten R, Otterbach F, Schmid KW. Erdheim-Chester disease: case report with multisystemic manifestations including testes, thyroid, and lymph nodes, and a review of literature. J Clin Pathol 2004;57:1225-8.
6. Myra C, Sloper L, Tighe PJ, McIntosh RS, Stevens SE, Gregson RH, et al. Treatment of Erdheim-Chester disease with cladribine: a rational approach. Br J Ophthalmol 2004;88:844-7.
7. Haroche J, Amoura Z, Trad SG, Wechsler B, Cluzel P, Grenier PA, et al. Variability in the efficacy of interferon-alpha in Erdheim-Chester disease by patient and site of involvement: results in eight patients. Arthritis Rheum 2006;54:3330-6.

8. Dickson BC, Pethe V, Chung CT, Howarth DJ, Bilbao JM, Fornasier VL, et al. Systemic Erdheim-Chester disease. Virchows Arch 2008;452:221-7.
9. Greenberger JS, Crocker AC, Vawter G, Jaffe N, Cassady JR. Results of treatment of 127 patients with systemic histiocytosis. Medicine (Baltimore) 1981;60:311-38.
10. Bancroft LW, Berquist TH. Erdheim-Chester disease: radiographic findings in five patients. Skeletal Radiol 1998;27:127-32.
11. Droupy S, Attias D, Eschwege P, Hammoudi Y, Benoit G, Jardin A. Bilateral hydronephrosis in a patient with Erdheim-Chester disease. J Urol 1999;162:2084-5.
12. Egan AJ, Boardman LA, Tazelaar HD, Swensen SJ, Jett JR, Yousem SA, et al. Erdheim-Chester disease: clinical, radiologic, and histopathologic findings in five patients with interstitial lung disease. Am J Surg Pathol 1999;23:17-26.
13. Haroche J, Cluzel P, Toledano D, Montalescot G, Touitou D, Grenier PA, et al. Images in cardiovascular medicine. Cardiac involvement in Erdheim-Chester disease: magnetic resonance and computed tomographic scan imaging in a monocentric series of 37 patients. Circulation 2009;119:e597-8.
14. Haroche J, Amoura Z, Dion E, Wechsler B, Costedoat-Chalumeau N, Cacoub P, et al. Cardiovascular involvement, an overlooked feature of Erdheim-Chester disease: report of 6 new cases and a literature review. Medicine (Baltimore) 2004;83:371-92.
15. Keenan N, Davies S, Sheppard MN, Maceira A, Serino W, Mohiaddin RH. Angiosarcoma of the right atrium: a diagnostic dilemma. Int J Cardiol 2006;113:425-6.
16. Luna A, Ribes R, Caro P, Vida J, Erasmus JJ. Evaluation of cardiac tumors with magnetic resonance imaging. Eur Radiol 2005;15:1446-55.
17. Veyssier-Belot C, Cacoub P, Caparros-Lefebvre D, Wechsler J, Brun B, Remy M, et al. Erdheim-Chester disease. Clinical and radiologic characteristics of 59 cases. Medicine (Baltimore) 1996;75:157-69.
18. Suzuki HI, Hosoya N, Miyagawa K, Ota S, Nakashima H, Makita N, et al. Erdheim-Chester disease: multisystem involvement and management with interferon-alpha. Leuk Res 2010;34:e21-4.
19. Breuil V, Brocq O, Pellegrino C, Grimaud A, Euller-Ziegler L. Erdheim-Chester disease: typical radiological bone features for a rare xanthogranulomatosis. Ann Rheum Dis 2002;61:199-200.
20. Perlat A, Decaux O, Sébillot M, Grosbois B, Desfourneaux V, Meadeb J. Erdheim-Chester disease with predominant mesenteric localization: lack of efficacy of interferon alpha. Joint Bone Spine 2009;76:315-7.