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Heart involvement in T cell lymphoma through hypereosinophilic syndrome: a common complication of a rare condition

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This case describes a 42-year-old male affected by hypereosinophilic syndrome associated with angioimmunoblastic lymphoma. Heart involvement was suspected at ECG mimicking left ventricular hypertrophy. MRI clarified the extensive endomyocardial fibrosis, confirming the role of this technique in in-vivo tissue characterization. Finally, the study investigates the association of T cell lymphoma, hypereosinophilic syndrome, and Loeffler endomyocardial disease.

Key Words: Hypereosinophilic syndrome; Endomyocardial fibrosis

1. Introduction

Endomyocardial fibrosis is a common complication of hypereosinophilic syndrome—a relatively rare disease in western countries (1).

Heart damage seems to be related to a direct tissue injury produced by toxic eosinophil granule proteins. This association of eosinophilia and severe heart failure was first reported by Loeffler in 1936 (2); however, to date the mechanism of eospinophils degranulation and the endocardial susceptibility is still scarcely understood (3, 4).

Cardiac damage generally features a subacute or chronic course with restrictive pattern, but cases of acute onset with severe systolic ventricular failure and high mortality rate have also been reported (5, 6). Moreover, Mosuez et al. have reported the association of T cell lymphoma, hypereosinophilic syndrome, and Loeffler endomyocardial disease (7).

So far, echocardiography has been the most effective first-line tool in the diagnosis of endomyocardial fibrosis (8). Yet more recently, computed tomography and particularly magnetic resonance imaging (MRI) have demonstrated to allow a more comprehensive characterization of the heart involvement (9, 10).

2. Report of a case

A 42-year-old Caucasian male with abdominal pain underwent an abdominal echo scan, which showed confluent massive lymph nodes. The results of blood tests were: red blood cell count 4.980.000/mm3, hemoglobin 15.7 g/L, hematocrit 43.5%, mean cell volume 87.3 fL (femtoliter), and white blood cells 28.000/dL, (neutrophiles 1.4%, lymphocytes 3.5%, eosinophiles 79.6%, basophiles 0.4%). Erythrosedimentation velocity was 22 mm/h. Fibrinogen was 475 mg/dL, aspartate amino transferase/alanine amino transferase (AST/ALT) 22/21, lactic dehydrogenase (LDH) 702 U/L, and plasma proteins 7.6 g/dL. Carcino embryonic antigen, alpha feto protein, gastrointestinal carcinoma antigen (GICA), and tumor protein antigen were within normal limits. Markers for hepatitis ABC and human immunodeficiency virus (HIV) were negative.

Because no superficial lymph nodes were available for biopsy, an ECG was recorded as a screening test for the laparoscopic biopsy. The ECG unexpectedly showed a left ventricular hypertrophic pattern different from the normal ECG the patient had a year earlier (Fig. 1).

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Physical examination demonstrated a third heart sound, lung examination was normal, no peripheral edemas or jugular distension were present: blood pressure was 100/70 mmHg, and heart rate was 100 bpm.

The systolic function of both ventricles was normal at echocardiography; however, the apex of the left ventricle was thickened, almost obliterated during systole, and the transmitral Doppler flow showed a restrictive pattern (Fig. 2). A mild mitral insufficiency was also present.

Finally, magnetic resonance imaging (MRI) of the heart was obtained (Fig. 3).

MRI images were obtained by 1.5 T scanner (GE, CVi, Milwaukee, WI) using the following sequences: SE T1 (matrix 256 × 192, TR 541 msec, TE 25 msec, FA 90°, 2 NEX, thickness 8 mm) before and after gadolinium-based contrast agent (0.1 mmol/kg); short inversion-time inversion recovery (triple IR) (matrix 256 × 224, TR 1008 msec, TE 69 msec, TI 150 msec, FA 90°, 1 NEX, thickness 8 mm); cine (30 phases) steady-state free precession sequence (FIESTA) (matrix 256 × 224, TR 4.1 msec, TE 1.7 msec, FA 45° 1 NEX, thickness 8 mm), segmented inversion recovery (delayed enhancement) (TR 6.6 msec, TE 1.5 msec, FA 20°, prep time 250 msec, matrix 256 × 160, 2 NEX, slice thickness 10 mm) after an adjunctive contrast agent administration (a total of 0.2 mmol/kg).

The material obliterating the apex of the left ventricle was interpreted as fibrous tissue and thrombotic material. A thin subendocardial fibronecrotic layer was also evident (Fig. 3).

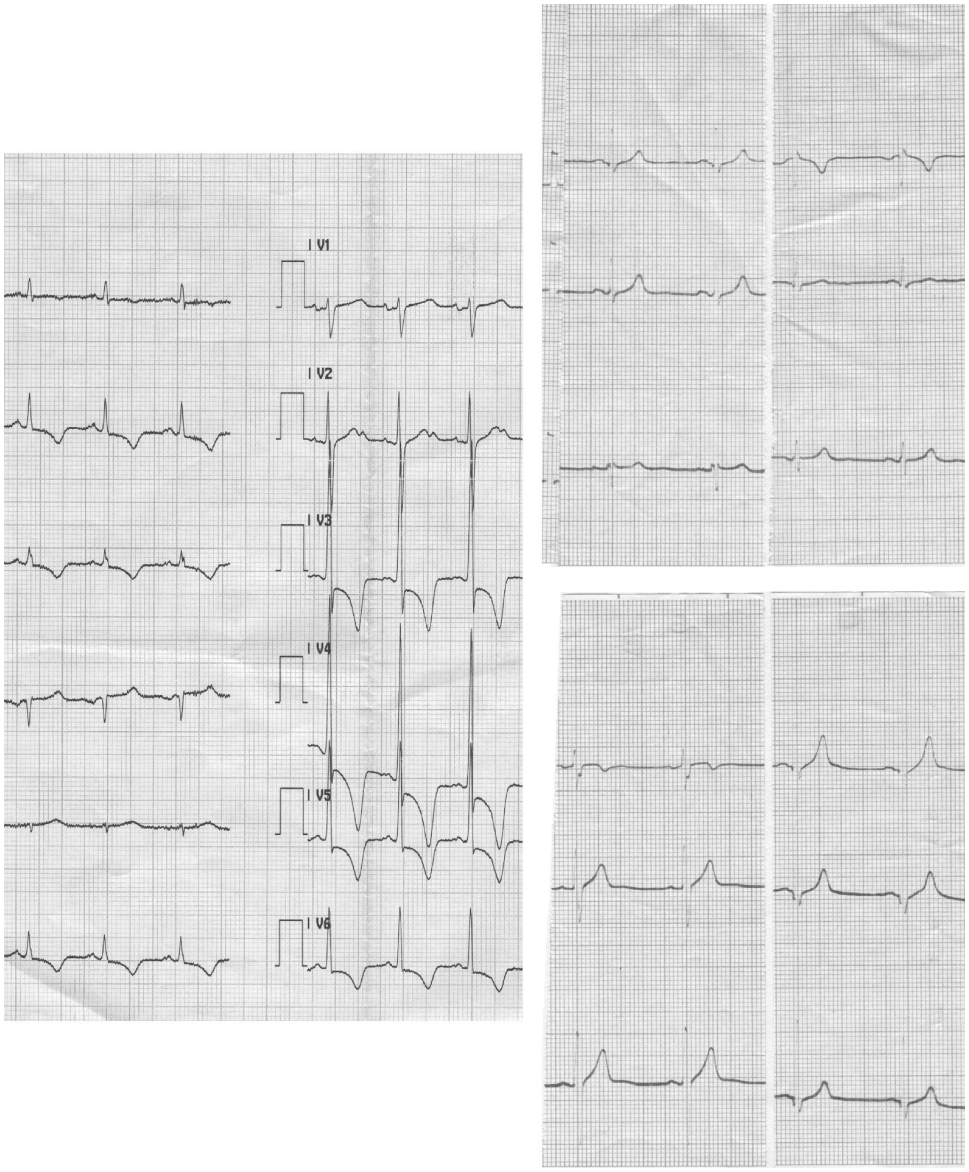

Figure 1. Twelve-lead electrocardiogram recorded at presentation (right panel) and less than 12 months earlier (left panel).

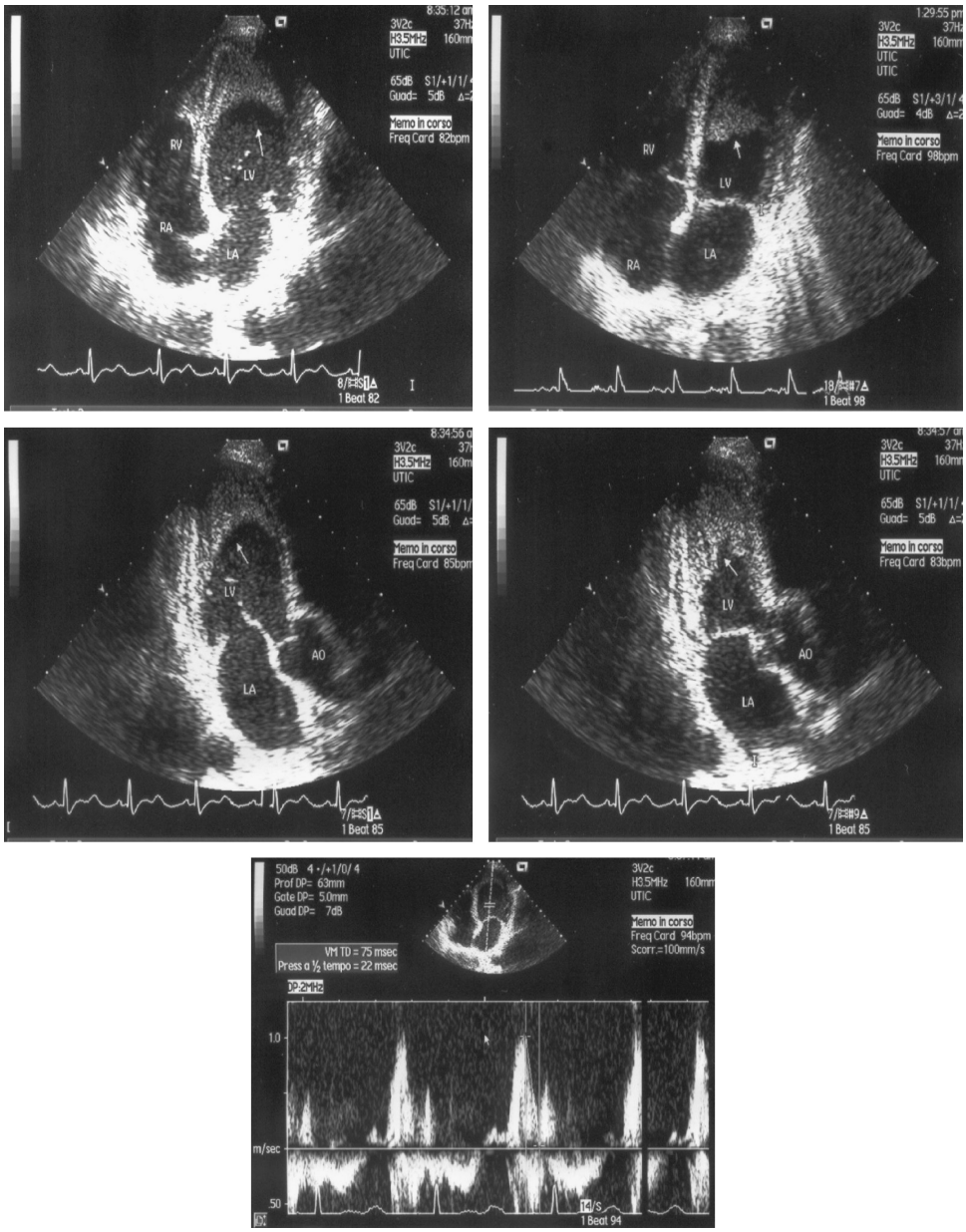

Figure 2. Echocardiographic and Doppler findings. Upper panels: four-chamber apical view. End-diastole (left), end-systole (right). Mid panels: three-chamber apical view. End-diastole (left), end-systole (right). The arrows indicate the endocardial thickening of the apex. Lower panel: transmitral flow with high E peak, low A peak, and short deceleration time of E peak, which represents a restrictive inflow pattern.

The biopsy specimens are showed in Fig. 4.

These results suggest a diagnosis of angioimmunoblastic lymphoma complicated by Loeffler endomyocarditis. Endomyocardial biopsy was not planned because of the poor clinical conditions of the patient.

The patient received a third-generation regimen of chemotherapy: prednisone, doxorubicin, cyclophosphamide, and etoposide, followed by cytarabine, bleomycin, vincristine, and methotrexate with leucovorin rescue, according to the ProMACE CytaBOM protocol (11).

One month later, *Pneumocystis carinii* pneumonia was diagnosed. Treatment with tazobactam, high dose piperacillin, and fluconazol was administered unsuccessfully and the patient died.

3. Discussion

Angioimmunoblastic lymphoadenopathy is a rare condition, which affects more often elderly patients. It is characterized by fever, muscle pain, night diaphoresis, liver and spleen enlargement, skin rashes, hypergammaglobulinemia, anemia—often associated with Coombs positivity, and hypereosinophilia.

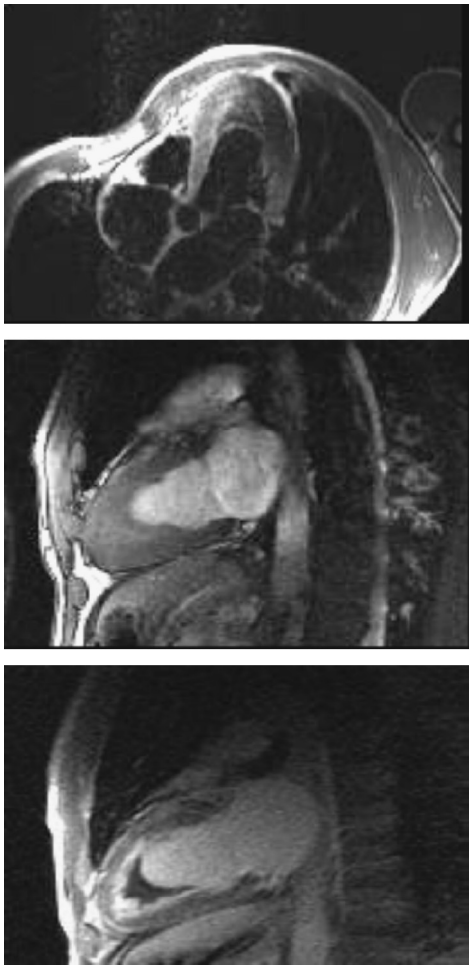

Figure 3. MRI findings. Upper panel: spin echo image in horizontal long axis. Middle panel: Cine FIESTA image in vertical long axis. Lower panel: image obtained with a delayed enhanced sequence after injection of gadolinium-based contrast agent. The apical wall is thickened by the presence of fibronecrotic material (showing an enhanced pattern) and by thrombotic material (showing a hypointense pattern).

The hypereosinophilia is due to cytokines produced by T lymphocytes, particularly IL-5 but also IL-2 and IFN γ 12 and is usually moderate, very rarely exceeding 5×10^9/L (13).

About 30% of patients with hypereosinophilia develop an angioimmunoblastic lymphoma that has surface receptors for T lymphocytes. The syndrome is a collection of several entities such as allergic diseases, parasitic infections, eosinophilia-myalgia syndrome, Churg Strauss syndrome, malignancy, and idiopathic hypereosinophilic syndrome. When this latter complication occurs, eosinophils can infiltrate multiple organs and cause multiple organ dysfunction because of its granules containing toxic cationic proteins, which are the primary mediators of tissue damage. These toxins include major basic protein eosinophil peroxidase, eosinophil-derived neurotoxin, and eosinophil cationic protein. Eosinophils also release specific cytokines that recruit additional eosinophils, thus advancing the cycle of tissue damage and modulating the immune response. Additional damage is caused by oxidative products from the respiratory burst pathway of the infiltrating eosinophils. How and what triggers degranulation of circulating eosinophils in hypereosinophilic syndrome is still unknown.

The most serious complication deriving from hypereosinophilic syndrome is cardiac damage, which likely occurs with an initial acute necrosis, and evolves into a thrombotic phase, and lastly into endomyocardial fibrosis (14).

However, to the best of our knowledge, hypereosinophilic syndrome with a clear heart involvement is very rarely associated with specific angioimmunoblastic lymphoma. Yet, MRI of our patients clearly depicted heart involvement, showing that the apical wall thickening was due to both fibronecrotic and thrombotic material. This excluded apical

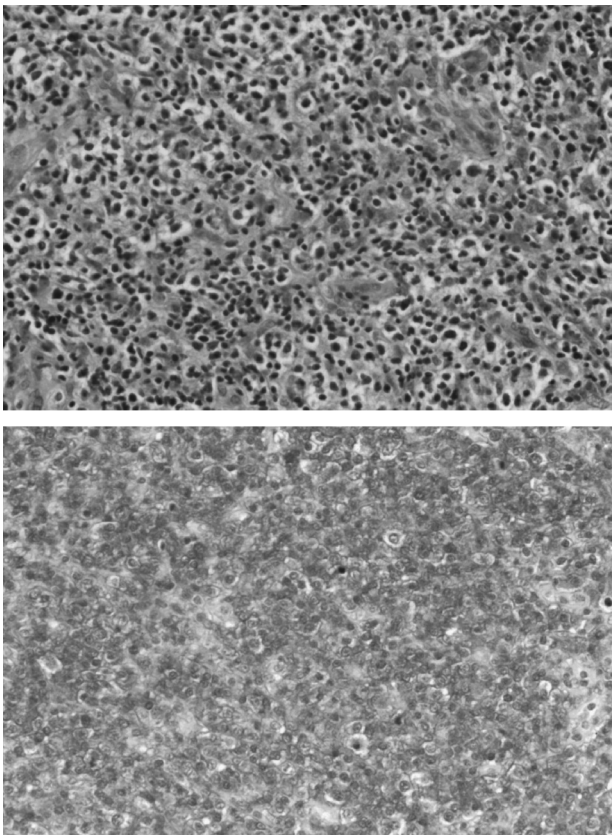

Figure 4. Biopsy specimens. Upper panel: complete substitution of the lymph node architecture by medium size lymphocytes, accompanied by small venules-capillaries and plasma cells proliferation. Numerous polymorphonuclear eosinophils are scattered in all the sections. Lymphoid cells show a pale white cytoplasm, which appears as an empty space in the microphotograph. They are organized in sheets and nests. The nuclei are small, round, and slightly irregular (ematossilin-eosin stain). Lower panel: immunohystochemical examination. Expression of T cell antigens CD3 in the neoplastic cells. The cytoplasm and the cytoplasmic membrane of T cells are deeply colored in orange-brown. Peroxidase-antiperoxidase (PAP) carbazole stain.

hypertrophic cardiomyopathy or simple apical thrombotic mass of unknown origin.

The correct diagnosis of heart involvement in the hypereosinophilic syndrome, which would have benefited the management of the patient, was unfortunately—in our case—of little help because of the rapid clinical course of the disease.

MRI was crucial in defining the extension of endomyocardial fibrosis; the segmented inversion recovery sequence showed the highest contrast between myocardium, fibronecrotic tissue, and thrombotic material. On the one hand, the thrombus appeared as a dark area inside the left ventricular cavity, whereas the subendocardial fibronecrosis demonstrated a high intensity signal. However, because in the present case autopsy was not performed, a certain level of uncertainty about the endocardial damage still remains. It can be speculated that fibrosis as well as necrosis can be found as a consequence of the disease (15). On the other hand, in the SE, as well in cine FIESTA images, the thrombus gave a hypointense pattern.

In conclusion, this case underlines two important issues. From a clinical perspective, this study reveals how rapidly the endomyocardial damage can appear in the presence of a severe hypereosinophilic syndrome. From an imaging perspective, this case demonstrates that magnetic resonance gives adjunctive insight for in vivo tissue characterization of endomyocardial disease.

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