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Presumed hydrochlorothiazide-associated immunologic-hypersensitivity-induced pericardial effusion

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Abstract

A 50-year-old Caucasian female presented for a second opinion regarding a newly diagnosed pericardial effusion. Seven months previously, hydrochlorothiazide was introduced into her pharmacologic regimen to aid in the management of her hypertension. A routine echocardiogram indicated a large pericardial effusion with signs of early cardiac tamponade. The patient subsequently underwent successful pericardiocentesis with complete drainage of the pericardial effusion. The effusion was empirically attributed to a viral etiology. Repeat echocardiograms showed recurrence of the pericardial effusion. Prior to undergoing a second pericardiocentesis with pericardial biopsy, as her physicians recommended, the patient sought a second opinion. While obtaining the patient's history, an allergy to sulfa was elicited. The possibility that the pericardial effusion may be secondary to an immunologic-hypersensitivity reaction was considered. It was recommended the patient discontinue the use of hydrochlorothiazide. Nine days following discontinuation of hydrochlorothiazide and without any other intervention, an echocardiogram was reported to show the size of the pericardial effusion had subsided substantially. Nine weeks following discontinuation, almost complete resolution of the pericardial effusion was reported. It is hypothesized that when treated with hydrochlorothiazide, the patient had an immune response leading to the pericardial effusion.

Keywords

Pericardial effusion, immunologic-hypersensitivity, sulfa Query

A 50-year-old Caucasian female with a past medical history significant for melanoma, resected 8 years previously without recurrence, as well as hypertension presented for a second opinion regarding a newly diagnosed pericardial effusion. Seven months previously, hydrochlorothiazide (6-chloro-1,1-dioxo-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide) was introduced into her pharmacologic regimen by her primary care physician to aid in the management of her hypertension. Three months thereafter, a routine echocardiogram—obtained as part of her primary care physician's evaluation given her diagnosis of hypertension—indicated a large pericardial effusion with signs of early cardiac tamponade (Figure 1). A repeat echocardiogram completed 3.5 weeks following the initial echocardiogram confirmed this finding. The patient subsequently underwent pericardiocentesis. Follow-up echocardiography performed 10 days following the pericardiocentesis showed successful and complete drainage of the pericardial effusion (Figure 2). The pericardial fluid obtained was reported to be without evidence of infection or carcinoma (Table 1). Rheumatologic evaluation was also reported to be negative (Table 2). The effusion was empirically attributed to a viral etiology. A repeat echocardiogram was performed 6 weeks post-pericardiocentesis to assess for any recurrence of the effusion. It was reported that the patient had small-sized reaccumulation of the pericardial effusion (Figure 3). As the patient was asymptomatic, it was elected to repeat the echocardiogram after 5 weeks. This showed the pericardial effusion had increased in size and was now described as moderate to large in size and circumferential (Figure 4). Another echocardiogram, performed 6 weeks after the finding of reaccumulation and 1 week after noting the reaccumulation had enlarged, again reported a moderate-to-large sized circumferential pericardial effusion without tamponade physiology. Her physicians recommended a repeat pericardiocentesis with pericardial biopsy.

Prior to undergoing a second pericardiocentesis with pericardial biopsy, the patient sought a second opinion. While obtaining the patient's history, an allergy to sulfa was elicited. The patient was asymptomatic and had no clinical signs or

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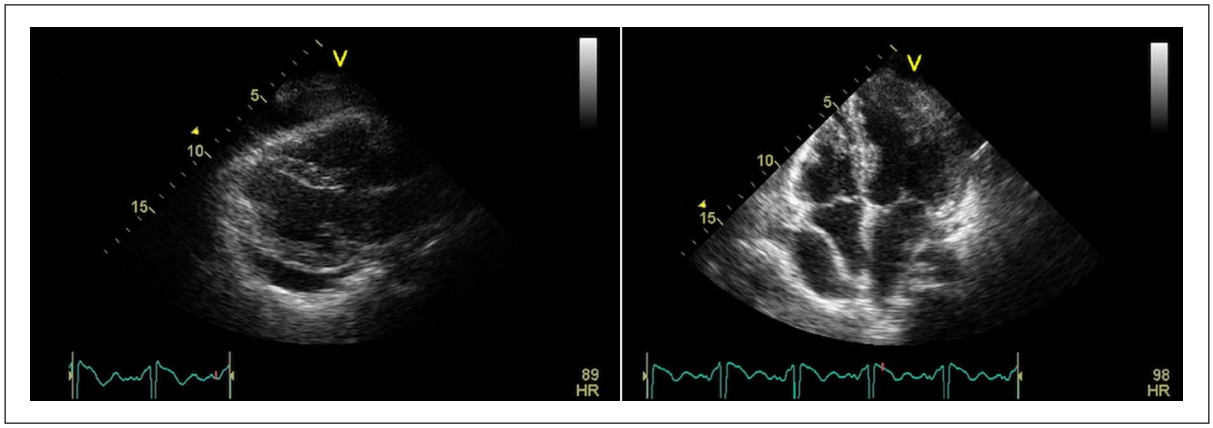

Figure 1. Initial Diagnosis.

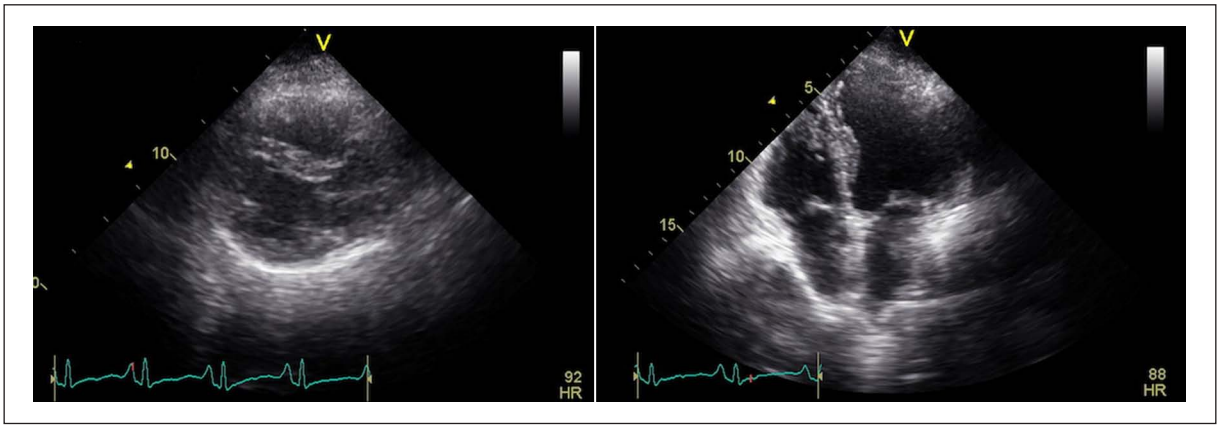

Figure 2. Post-pericardiocentesis.

Table 1. Pericardial fluid lab values.

Glucose	104
pH	8.0
Protein	4.5
LD	226
Nucleated cells	9253
RBC	29,536
Fungal culture	No growth
Anaerobic culture	No growth
Acid-fast bacillus culture	No growth
Acid-fast bacillus stain	Negative
Flow cytometry	Negative. No monoclonal B-cell population detected
CD4/CD8 ratio	Normal
Cytology	Negative including that for melanoma
Melanoma markers	
HMB45	Negative
Melon A	Negative
S-100	Negative

RBC: red blood cell; HMB: human melanoma black; CD: cluster difference; LD: lactic dehydrogenase.

Table 2. Rheumatologic lab values.

CRP	3
ESR	22
Angiotensin-1-converting enzyme	31
ANA	Negative
Thyroid function test	Normal

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ANA: antinuclear antibody.

symptoms of tamponade. As hydrochlorothiazide contains a sulfonamide group, the possibility that the pericardial effusion may be secondary to an immunologic-hypersensitivity (allergic) reaction was considered. It was therefore recommended the patient discontinue the use of hydrochlorothiazide. Nine days following discontinuation of hydrochlorothiazide and without any other intervention, an echocardiogram was reported to show the size of the pericardial effusion had subsided substantially. Nine weeks following discontinuation of hydrochlorothiazide, another echocardiogram was performed. Almost complete resolution of the pericardial effusion was

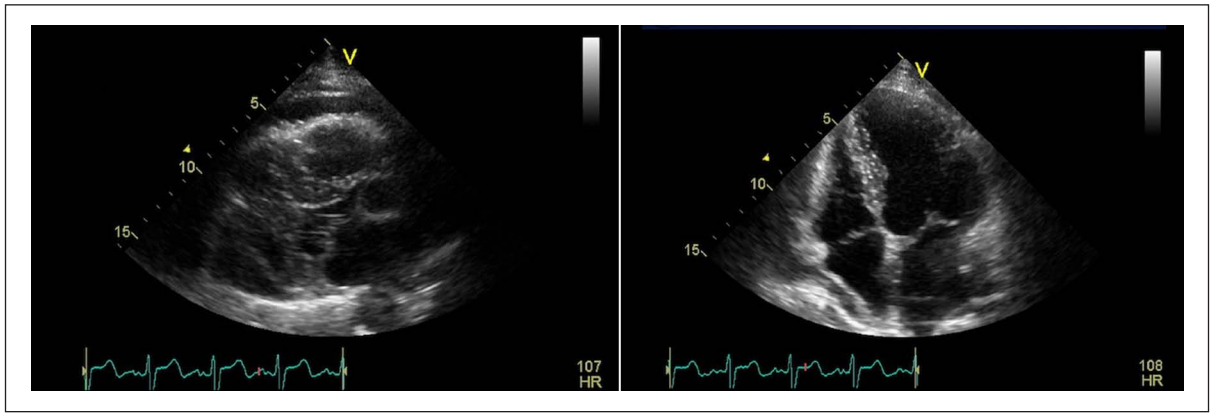

Figure 3. Reaccumulation of pericardial effusion.

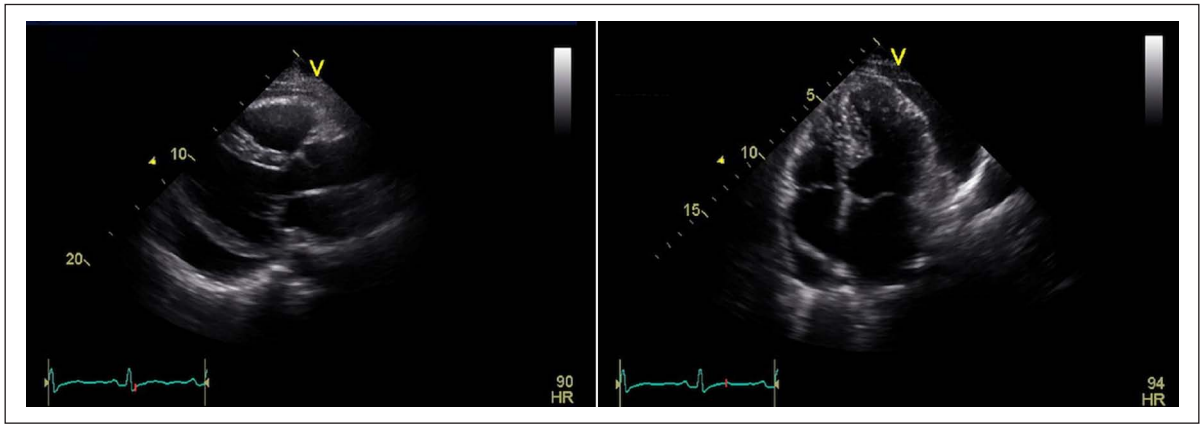

Figure 4. Increased pericardial effusion.

reported (Figure 5). It is therefore hypothesized that the pericardial effusion seen in this patient with a well-documented sulfa allergy was a manifestation of an immunologic-hypersensitivity reaction to hydrochlorothiazide.

There are case reports that implicate hydrochlorothiazide as the causal agent of life-threatening allergic reactions.[1,2] Additionally, the literature suggests that drug- and toxin-related pericardial disease might be caused by an "idiosyncratic" or hypersensitivity reaction.[3] Listed among the offending agents are sulfa drugs.[4] However, a review of the literature failed to reveal a specific case report and does not adequately hypothesize its pathogenesis in relation to pericardial effusion.

As evidenced by the patient's clinical course, our proposed mechanism is that the pericardial effusion was caused by an immunologic reaction to the sulfonamide group contained in hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$). Therefore, it is our hypothesis that when treated with hydrochlorothiazide, the patient had an immune response leading either to an immunoglobulin G (IgG)-mediated response, which induces a complement pathway, or an immunoglobulin E (IgE)-mediated response, which induces a mast cell activation. The former is an example of an Arthus-type reaction. In addition, one cannot exclude the possibility that this is a type-IV immunologic-hypersensitivity reaction mediated by T cells. The immune complexes bind the Fc receptors on mast cells and other leukocytes generating a local inflammatory response and increased vascular permeability. Fluid and cells, including polymorphonuclear leukocytes, can enter the site of inflammation (the pericardium) from local blood vessels. The immune complexes activate complement, producing complement fragment C5a. This then interacts with C5a receptors on the leukocytes, so that they become activated and are attracted to the site of inflammation. Once activated, the mast cells induce inflammatory reactions by secreting pharmacologic mediators such as histamines stored in preformed granules. They also synthesize prostaglandins, leukotrienes, and platelet-activating factor from the plasma membrane. In addition, cytokines and chemokines are released after activation. This leads to increased blood flow and increased permeability. Immunologic activation of these mast cells thus has an important physiologic consequence, conceivably leading to the pericardial effusion.[5]

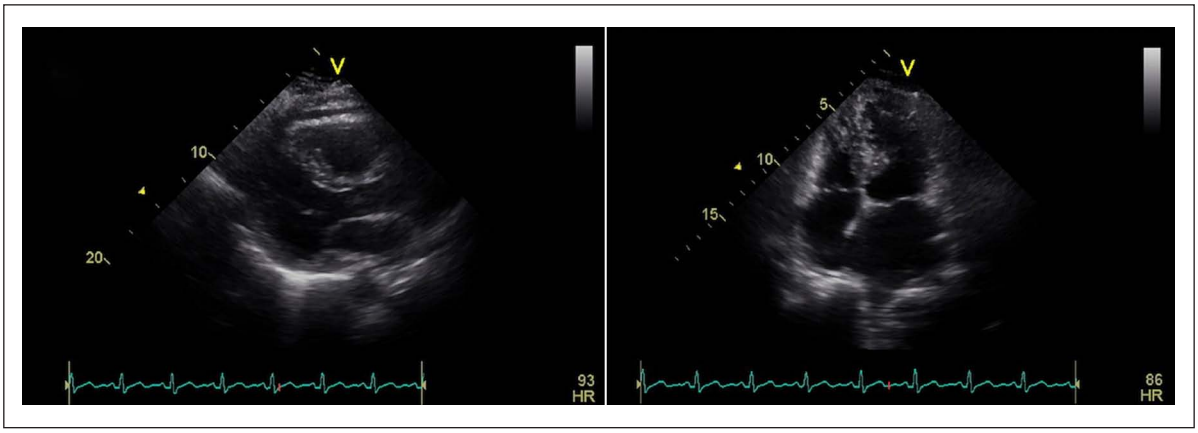

Figure 5. Resolution of pericardial effusion after stopping hydrochlorothiazide.

Withdrawal of the offending agent resulted in the resolution of the pericardial effusion. Unfortunately, there was no pericardial fluid preserved for further immunologic testing. While in vitro tests such as histamine release test, leukocyte transformation test, lymphocyte toxicity assay, and the recently described in vitro platelet toxicity assay could have been performed on this patient, these tests have not yet been validated to substantiate sulfa allergy and were therefore not conducted.[6] In this patient, the only way to prove that hydrochlorothiazide was the offending agent is to rechallenge her with hydrochlorothiazide. However, due to ethical considerations, this cannot be done. Using the Naranjo probability scale, it is probable that hydrochlorothiazide was the etiologic agent responsible for the patient's pericardial effusion.[7]

We would urge our colleagues, when faced with a pericardial effusion whose etiology is unknown, to review the patient's medications carefully and remove any potential antigens, which may be causing an immunologic-hypersensitivity reaction. If pericardiocentesis with or without a pericardial window is performed, we would recommend sending all fluid and tissue obtained for evaluation of possible drug-specific antibodies in addition to cytology, pathology, and virology, which is now the standard of care.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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