

CASE REPORT

A case of fatal perimyocarditis due to a rare disease

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Accepted: 7 September 2017
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Abstract Although myocarditis is caused by viral infections in about 50% of cases in European countries, various other causative agents are known. We report the case of a 51-year-old man who died several months after being diagnosed with asthma by his general practitioner. This diagnosis had been confirmed by a pulmonologist approximately 6 weeks before the man's death. To rule out the possibility of medical malpractice the prosecuting authority ordered a forensic autopsy. At autopsy macroscopic indicators for perimyocarditis and pneumonia were found. Microbiological and histological examination of tissue samples confirmed a diagnosis of Churg-Strauss syndrome, also known as Eosinophilic Granulomatosis with Polyangiitis (EGPA). The cause of death was determined to be cardiac involvement in Churg-Strauss syndrome. The presence of this disease also accounted for the man's recent medical history. There were no findings to indicate that a medical error had been made. The reported case illustrates why accessory histological and microbiological examinations should always be performed when macroscopic findings at autopsy suggest myocarditis. Determining the etiology of myocarditis is a necessary step to prevent overlooking rare diseases with inflammatory myocardial involvement, especially in the clarification of alleged medical malpractice.

Keywords Churg-Strauss syndrome · EGPA · Myocarditis · Medical malpractice assessment · Rare disease

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Introduction

Myocarditis is one of the more common causes of death diagnosed at autopsy in cases of sudden unexpected deaths in younger to middle-aged individuals. In Europe, the most frequent cause of myocarditis is viral infection, but various other causative agents are also known ([1–3], Table 1).

As death due to myocarditis is sudden and unexpected, it is likely that forensic autopsies will be performed on a certain percentage of cases with this underlying condition [4]. It is not unusual for individuals with myocarditis to experience unspecific complaints days or weeks before their death, which, in some cases, may lead them to consult a doctor. When they unexpectedly die, despite, or shortly after, consulting their doctor, the occurrence of this consultation shortly before death often prompts the investigation of a medical malpractice claim. The validity of such a claim can only be satisfactorily assessed by performing a forensic autopsy. Accessory histological examination of tissue samples is essential, particularly when myocarditis is the suspected cause of death, as myocarditis can only be confirmed by histology. Accessory microbiological analysis may also be necessary for further diagnostic differentiation.

Case report

A 51-year-old man, who had attended a birthday party the previous night, was found dead the next morning by a female relative. He was sitting in the driver's seat of his car, which was parked on the side of the road. An asthma spray inhaler (Formoterol) was found on the front passenger seat. The emergency doctor who had been called to the scene attested the cause of death to be unknown.

Table 1 [According to 1–3]: causative agents for myocarditis

Infection	Viruses (50% of cases; e.g., <i>Enteroviruses</i> , <i>Influenza viruses</i> , <i>Adenoviruses</i> , <i>Parvovirus B19</i>), Bacteria (e.g., <i>Streptococcus sp.</i> , <i>Staphylococcus sp.</i> , <i>Borrelia burgdorferi</i>), Fungi (e.g., <i>Aspergillus sp.</i> , <i>Candida sp.</i>), Protozoa (<i>Toxoplasma sp.</i> , <i>Trypanosoma sp.</i>), Parasites (e.g., <i>Echinococcus sp.</i>)
Pharmacological/toxic	e.g., doxorubicin, lithium, cocaine
Physical	e.g., radiation, hypothermia
Allergy/hypersensitivity	e.g., penicillin, sulfonamide, tricyclic antidepressants
(Systemic) disorders	e.g., vasculitis (e.g., Churg-Strauss syndrome), collagenosis (e.g., systemic lupus erythematosus), rheumatoid arthritis

The man had last been seen alive at the party the evening before. According to relatives' reports to the police, the man had unintentionally lost 10–15 kg during the previous eight weeks and had complained about a globular sensation in his throat, close to his larynx. He had also been occasionally complaining about wheezing. About five months earlier, in the spring, he had complained of dyspnea, particularly during physical exertion or when exposed to dust. The man had subsequently stopped smoking and had visited his family physician, who had diagnosed him with asthma and given him a prescription for Symbicort (Budesonid/Formoterol). The use of this medication had alleviated the complaints. At an appointment with a pulmonologist in the late summer, an allergy prick test was performed. The results of this allergy test showed a marked positive response in particular to mold spores, grass pollen, and early bloomer pollen. On auscultation of the lungs, a faint bilateral rhonchus that did not entirely disappear after coughing could be heard. A lateral thoracic radiograph showed lung areas with a slight increase in radiotransparency, possibly as a sign of emphysema, but no other conspicuous findings. Full-body plethysmography revealed significant obstruction of the airways, particularly in the peripheral regions. A FeNO measurement of 35 ppb (normal reference value: < 25 ppb) further supported a diagnosis of allergic asthma. In a FeNO test (fractional exhaled nitric

oxide), the concentration of nitric oxide in a subject's exhaled breath is measured. Because nitric oxide is, in particular, produced by inflammatory response cells, the concentration of nitric oxide in exhaled breath reflects the degree of inflammation.

A differential blood count showed a significant rise (14%) in eosinophilic granulocytes. Historical medical files from the man's family physician revealed that he had been diagnosed with an allergy, for which a cortisone-containing ointment had been prescribed, many years prior to receiving the recent asthma diagnosis.

The prosecuting authority ordered a forensic autopsy to clarify the cause of the man's death and to assess the possibility of a medical error having been made. The most prominent finding at autopsy was the indication of inflammatory changes in the heart (Fig. 1). The surface of the section through the myocardium was inhomogeneous in appearance, with regions of pallor and small hemorrhagic areas in the muscle tissue. The heart was coated in a grayish-yellow, in part, opaque, film. Small to medium subpericardial hemorrhages were present in some areas. A streaky, yellowish-red effusion was found in the pericardium. The lung tissue (Fig. 2) showed areas of increased brittleness, in addition to appearing dappled, and, in some regions, highly compacted. A nutmeg liver was present. No pathogens were found in the accessory microbiological and virological examinations performed on samples of heart blood, or from samples and swabs of heart and lung tissue. Chemico-toxicological analysis demonstrated ibuprofen in a therapeutic concentration in a sample of femoral vein serum;

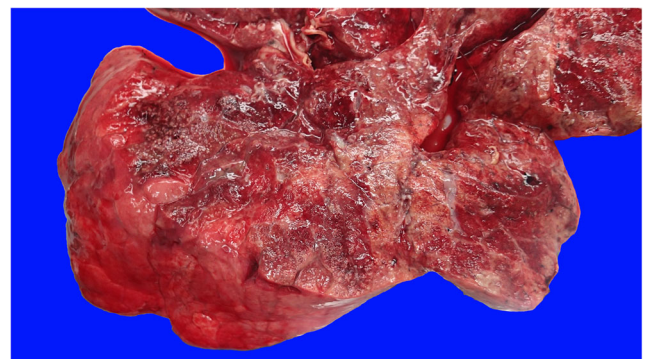
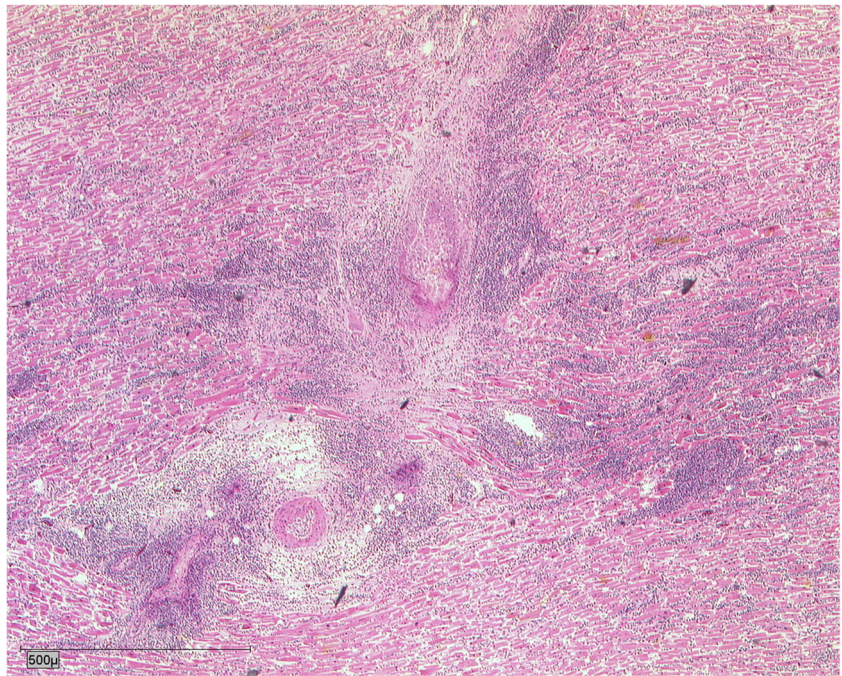
**Fig. 1** Inflammatory changes in the pericardium**Fig. 2** Macroscopic findings indicative of inflamed lung tissue

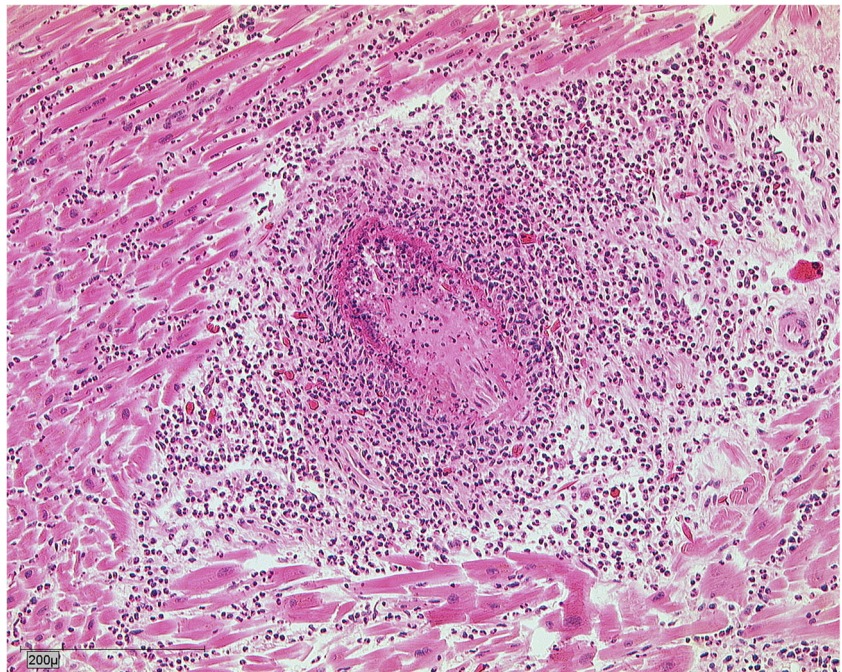
Fig. 3 Infiltration of myocardial tissue by eosinophilic granulocytes; overview. HE-stain (hematoxylin-eosin)



no other medications or drugs were detected. Blood and urine samples were negative for alcohol.

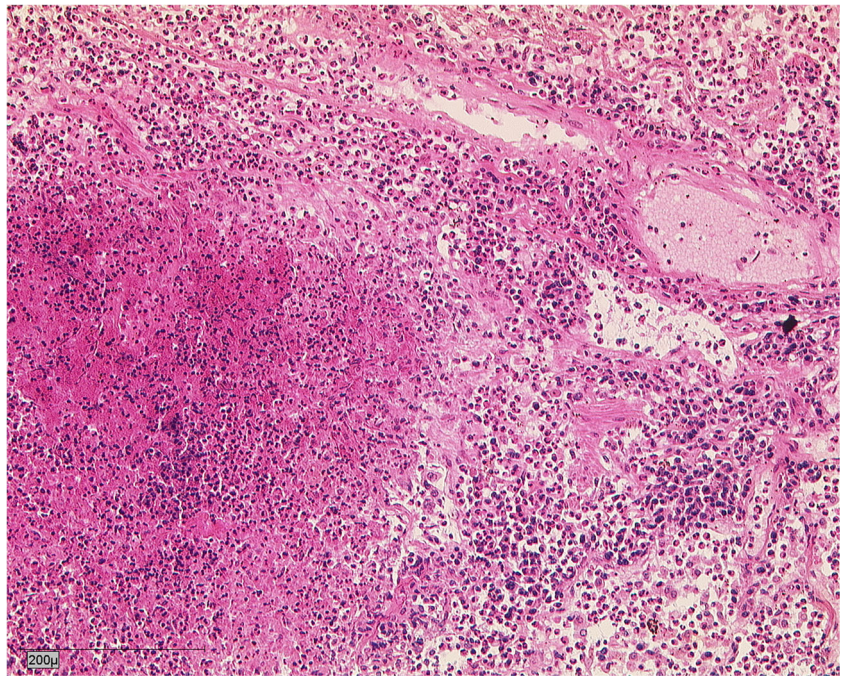
During accessory histological examination of tissue samples from all parenchymatous organs, marked infiltration of eosinophilic granulocytes was found in the heart samples, not only disseminated throughout the myocardial tissue, but also in high concentration in and around the walls of smaller intramyocardial vessels. In some regions, the eosinophilic granulocytes were arranged in a granuloma-like pattern, most notably in necrotic regions of the vessel walls (Figs. 3 and 4).

Fig. 4 Infiltration of myocardial tissue by eosinophilic granulocytes; detail. HE-stain



Some of the vessel cavities were thrombosed. Eosinophilic abscesses and epithelioid cell granulomas were also found in lung tissue samples, with occasional aggregations around small and middle-sized lung arterioles; in places, the vessel walls had necrotic areas (Fig. 5). Furthermore, edematous changes could be observed in the lung tissue, especially in peripheral regions, along with inflammatory eosinophilic infiltration of the bronchioles. Numerous eosinophilic granulocytes were found in spleen samples, as well as in liver samples, where aggregations of eosinophilic granulocytes

Fig. 5 Inflammatory eosinophilic lung infiltrate showing granuloma-like arrangement and necrosis. HE-stain



were found in the periportal space. Mild infiltration was also present in kidney samples.

In view of all of the findings, the cause of death was determined to be eosinophilic perimyocarditis in Churg-Strauss syndrome.

Discussion

Churg-Strauss syndrome (CSS) is a systemic necrotizing eosinophilic granulomatous inflammatory disease affecting small to medium-sized vessels. With an incidence of 1–3 cases per 1 million individuals per year, Churg-Strauss syndrome is a rare disease [5] that is usually diagnosed with the help of criteria established by the American College of Rheumatology (ACR, [6], Table 2). At least four of the seven ACR criteria need to be met to allow a diagnosis of Churg-Strauss syndrome [6]. The sensitivity of this diagnosis according to these

criteria is given as 85%, while the specificity is given as 99.7% [7].

Churg-Strauss syndrome usually manifests around middle age and affects men slightly more often than women [5]. Frequently, the symptoms of Churg-Strauss syndrome are initially unspecific (sometimes over a period of months or years), with the development of asthma, either in conjunction with, or without, allergic rhinitis, and nasal polyps [7]. Later, involvement of other organs, such as the heart and gastrointestinal tract, may also occur with accordingly typical symptoms [7]. Cardiac involvement in the inflammatory process is associated with a poor long-term prognosis and is the leading cause of early death in this disease [7, 8]. In the early stages of Churg-Strauss syndrome cardiac involvement often remains inconspicuous [8, 9]. The gold-standard therapeutic approach to treating Churg-Strauss syndrome is to administer a regimen of high-dose corticosteroids, which may be combined with administration of cyclophosphamide, particularly when other organs are also involved [7, 10]. If this therapy, which delays the onset of organ damage, is started in the early stages of the disease, the prognosis is good [10], with a rate of 81–92% for complete remission of the disease in treated patients, and a total mortality rate for treated patients who suffered a relapse during treatment of 3.1% [10]. Another source places the 1-year survival rate of treated patients without organ involvement at 100%, and the 5-year-survival rate at 97% [7]. In contrast, the mortality rate for untreated patients is 50% within three months of diagnosis [7].

The striking difference in mortality rates between treated and untreated patients illustrates how important early diagnosis of this disease is. The presence of extravascular

Table 2 [According to 6]: ACR-criteria for Churg-Strauss syndrome

1. Asthma
2. Eosinophilia >10%
3. Atopic diathesis
4. Migratory pulmonary infiltrates
5. Mono- or polyneuropathy
6. Sinusitis, nasal polyps, rhinitis
7. Histological demonstration of extravascular eosinophils in biopsy samples

eosinophilic blood cells in biopsy samples currently appears to be the most relevant diagnostic criterion for CSS; however, because of the rarity of this disease, the cost-benefit ratio for this examination needs to be carefully weighed.

To preclude any confusion, we would, at this point, like to point out that the nomenclature of systemic vasculitides was revised in 2012: The older name, CSS, which we have used in this report and which will still be familiar to many readers, is now known as “Eosinophilic Granulomatosis with Polyangiitis” (EGPA) [11].

Differential diagnoses to CSS include other rheumatologic diseases, such as Perarteritis nodosa [8] and allergic asthma, which although also characteristic of CSS in the prodromal stage, is far more frequently encountered as an independent disorder. In view of confounding diagnoses such as the above, and the early diagnostic stage in our case, as well as the circumstance that myocardial involvement can remain clinically unapparent and, most importantly, the fact that the deceased individual had not sought further medical care in the six-week interval between his visit to the pulmonologist and his death, there was no medicolegal evidence of medical malpractice due to a misdiagnosis on the part of the pulmonologist.

Without the additional microbiological, and even more importantly, histological examination of tissue samples, it would not have been possible to correctly diagnose eosinophilic perimyocarditis in Churg-Strauss syndrome as the ultimate cause of the man's death in this case. Therefore, in case work assessing medical malpractice claims, at least histological examination of tissue samples should be routinely performed.

Key points

1. Churg-Strauss syndrome is characterized by systemic eosinophilic granulomatous vasculitis, which usually manifests as asthma in the prodromal phase.
2. In later stages, this disease can involve almost all of the organs. Life-threatening cardiac involvement (eosinophilic myocarditis) is frequently asymptomatic or manifests only minimal symptoms.
3. Whenever macroscopic autopsy results point to the possibility of myocarditis, a histological examination should

be performed to clarify its etiology; in particular in cases assessing medical malpractice claims.

4. Because of the high frequency of viral myocarditis cases, microbiological analysis of tissue samples should also be considered.

Acknowledgements Many thanks to Dr. med. M. Divo, Institute of Pathology, Klinikum Frankfurt-Höchst, Germany, for the expert assistance.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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