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Abstract: Cocaine is a well known trigger of acute coronary syndromes. Over the last 10 years levamisole, a veterinary anthelminthic drug has been increasingly used as an adulterant of cocaine. Levamisole was used to treat pediatric nephritic syndrome and rheumatoid arthritis before being withdrawn from the market due to its significant toxicity, i.e. hematological complications and vasculitis. The major complications of levamisole-adultered cocaine reported up to now are hematological and dermatological.

The case reported here is of a 25 year old man with a history of cocaine abuse who died at home after complaining of retrosternal pain. Postmortem CT-angiography, autopsy, and chemical and toxicological analyses were performed. An eroded coronary artery plaque was found at the proximal segment of the left anterior descending coronary artery. Two myocardial infarct scars were present in the left ventricle. Microscopic examination of the coronary artery revealed infiltration of eosinophils into the adventitia and intima. Toxicological examination confirmed the presence of cocaine and its metabolites in the peripheral blood, and of levamisole in the urine and pericardial fluid.

Eosinophilic inflammatory coronary artery pathologies have been clinically linked to coronary dissection, hypersensitivity coronary syndrome and vasospastic allergic angina. The coronary pathology in the presented case could be a complication of levamisole-adultered cocaine use, in which an allergic or immune-mediated mechanism might play a role. The rise in cocaine addiction worldwide and the increase of levamisole adulterated cocaine highlights the importance of updating our knowledge of the effects of adultered cocaine abuse.

Author Disclosures

Contributors

All authors contributed to the data collection, their analysis and interpretation. All authors have read and approved the final manuscript

Conflict of interest

There are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome

Title page

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Acute coronary syndrome after levamisole-adultered cocaine abuse

Abstract

Cocaine is a well known trigger of acute coronary syndromes. Over the last 10 years levamisole, a veterinary anthelminthic drug has been increasingly used as an adulterant of cocaine. Levamisole was used to treat pediatric nephritic syndrome and rheumatoid arthritis before being withdrawn from the market due to its significant toxicity, i.e. hematological complications and vasculitis. The major complications of levamisole-adultered cocaine reported up to now are hematological and dermatological.

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Introduction

Cocaine greatly influences the cardiovascular system and is a well known trigger of acute coronary syndromes. The toxic effects of cocaine are related to arterial vasoconstriction, accelerated atherosclerosis and thrombosis. The reported triggering pathways include activation of the sympathetic nervous system with a transient increase in blood pressure, heart rate, plaque activity, and arrhythmias. These changes can lead to plaque rupture, thrombosis and/or sudden death. [1, 2]

Cocaine use is increasing around the world and the drug is frequently altered by dilution, substitution, contamination and adulteration. [3, 4] Cocaine is adulterated in many ways, i.e. with local anesthetics and phenacetin. Levamisole was recognized as a cocaine adulterant in the United States in 2002. Since then the percentage of cocaine contaminated by levamisole in Europe and the United States rose steadily to reach approximately 69% in 2009. [5, 6] A clinical study, performed in 2010 in the United States on hospitalized patients with unexplained agranulocytosis or cutaneous vasculitis, showed that 83% of patients who tested positive for cocaine also tested positive for levamisole. [7]

Levamisole is a synthetic imidazothiazole derivate. It is the *levo enantiomer* of tetramisole. It has been principally used as a veterinary anthelminthic medication, but was also used to treat pediatric nephritic syndrome and rheumatoid arthritis before being withdrawn due to its significant toxicity. [3, 4, 8] Pharmacological effects on the

central nervous system are not completely understood, it was suggested that levamisol increases the number of D1 dopamine receptors in the brain and potentiate the intense "high" of cocaine. [4, 6, 9, 10] Sequelae of levamisole administration include leucopenia, agranulocytosis, leukoencephalopathy, arthritis, thrombotic vasculopathy and vasculitis (i.e. leucocytoclastic vasculitis and cutaneous necrotizing vasculitis). Levamisole may provoke hypersensitivity reactions in genetically predisposed individuals [9]. The principal complications reported in cocaine users are hematological (neutropenia) and dermatological in origin. [6, 11] Recent reports attribute levamisole adultered cocaine use with a wide variety of clinical manifestations that can be difficult to distinguish from idiopathic autoimmune rheumatic diseases [8, 9] with a high rate of recurrence (27%) of symptoms upon re-exposure to cocaine.[3] Several authors have suggested that levamisole-adulterated cocaine might be associated with other severe extracutaneous manifestations, and that it is clinically important to accurately identify levamisole-induced complications in order to adapt treatment modalities. [4, 5, 8, 12, 13]

In this article, we present a case of coronary artery disease in a young cocaine user, suggesting a new complication which has not yet been reported.

Case Report:

A 25 year old man, who was known to be a cocaine addict, died suddenly at home after complaining of retrosternal pain. The electrocardiogram performed by the rescue team showed ventricular fibrillation. A year prior to death the patient had presented to the emergency room with a Q-wave myocardial infarction. His blood lipids levels were normal. The patient refused coronarography and did not follow the prescribed treatment plan. He complained of pins and needles in the left arm, especially in the morning, and of retrosternal pain after an effort.

A complete postmortem examination was performed the day after he died.

External examination: The decedent was of average build and nutrition. He weighed 52 kg and had a BMI of 19. There were signs of resuscitation attempts (sternal fracture, and defibrillator and injection marks).

Post-mortem radiology: native (unenhanced) CT scan and multi-phase post-mortem CT angiography (MPMCTA) [14] were performed by a trained forensic radiographer [15] on an 8-row CT-unit (CT LightSpeed 8, GE Healthcare, Milwaukee, WI, USA) using the following scan parameters: field of view: 50 cm, slice thickness: 1.25 mm, interval: 1mm, 120 kV, 280 mA (modulated), tube rotation: 0.8 sec, pitch: 0.875. Peripheral blood, cerebrospinal and vitreous fluids, and hair samples for toxicological analysis were collected according to standard autopsy protocol prior to the injection of the contrast

agent. Samples of bile and urine were obtained under CT-guidance as described by Schneider et al. [16] MPMCTA, was performed using a Virtangio® perfusion device and the oily contrast agent Angiofil® (Fumedica AG, Switzerland) mixed with paraffin oil (paraffinum liquidum, obtained in the local pharmacy) at a ratio of 1:6. Cannulation was performed in the left inguinal region. Angiography was performed following the standard protocol of MPMCTA of Grabherr et al. [14] Scan parameters of the arterial phase were: field of view: 50 cm, slice thickness: 1.25 mm, interval: 0.6 mm, 120 kV, 280 mA (modulated), tube rotation: 0.8 sec, pitch: 0.875. For the venous and dynamic phases of MPMCTA, the following scan parameters were used: field of view: 50 cm, slice thickness: 2.5 mm, interval: 2 mm, 120 kV, 280 mA (modulated), tube rotation: 0.8 sec, pitch: 0.875.

Image interpretation was performed by two board certified radiologists; one specialized in vascular radiology the other in neuro-radiology, along with one board certified forensic pathologist trained in forensic imaging. A post-mortem radiological report was completed, describing all of the findings observed in native CT and in each phase of MPMCTA. Radiological findings included pulmonary edema and pleural effusion (Fig 1a), which was already visible in the unenhanced CT-scan. The arterial phase of PMCTA revealed pathological enhancement of the myocardium of the left ventricle and septum (Fig. 1a), as well as a luminal stenosis of the proximal portion of the left anterior descending artery (Fig 1b).

Forensic Autopsy: The heart weighted 330 grams (predicted heart weight according to Kitzman et *al* 213-371 grams[17] , and for the local population 207.5-378 grams http://calc.chuv.ch/Heartweight). The ventricles were dilated; the left ventricle thickness was 1.4 cm and the cardiac valves were unremarkable. A small eroded plaque was found in the proximal portion of the left anterior descending artery (LAD) (Fig 1c). There were two fibrous scars of healed infarction in the left ventricular myocardium (Fig 1d): a transmural scar in the anterolateral wall and a subendocardiac scar in the anterior part of the ventricular septum. Pleural effusion (250 ml on the right and 100 ml on the left) and pulmonary edema were present. The other organs were normal.

Histological analysis: Histological examinations were performed on the brain, lungs, kidneys, liver, myocardium and the proximal segment of the LAD using standard H&E and trichrome staining. Myocardial examination revealed fibrous tissue in the anterolateral wall and in the anterior septum. A few contraction bands were observed in the anterior wall. There was no eosinophilic infiltration in the myocardium and the intramural coronary arteries were free from inflammation. Microscopic examination of the proximal portion of the LAD artery showed fibrous thickening of the intima and an infiltration of numerous eosinophils into the adventitia and intima (Fig 2 a-b). A small amount of thrombotic material adhering to the eroded plaque was detected (Fig 2 c-d). Fibrinoid necrosis and granulomatous changes were not found in the inflammatory areas. No signs of vasculitis were observed in the other organs.

Toxicological analysis: The toxicological analyses of femoral blood obtained before radiological examination and performed by GC-MS revealed the presence of cocaine (340µg/L) and its metabolites (benzoylecgonine 610 µg/L, methylecgonine 210 µg/L). Screening analyses detected levamisole in the urine and pericardial fluid, and phenacetin in the pericardial fluid. No alcohol was detected. Cocaine was detected in the hair samples (9 ng/mg); the maximal hair length was 2 cm.

Postmortem laboratory investigations demonstrated a normal CRP level (less than 2 mg/L), elevated levels of troponin I (0.28 µg/L; normal < 0.04) and NT-proBNP (211 ng/L; normal < 115 ng/L) and tryptase at its upper limit (12.1 µg/L, normal < 13.5 µg/L).

Discussion

An acute coronary event can result from numerous conditions, for example rising catecholamine and cortisol levels, exposure to toxins and drug intake. [18] Cocaine is a well known trigger of acute coronary syndromes [2, 19, 20] and vasculitis is a well-described complication of cocaine use. The presence of increased numbers of adventitial mast cells has been reported in cocaine abusers [21], as well as eosinophilic myocarditis. [22] Eosinophilic coronary inflammation, however, has not been previously reported in cocaine users. Churg-Strauss vasculitis with biopsy-proved eosinophilic infiltrates in small arteries and venules has been reported in one case of an adult cocaine user by Orriols *et al* but toxicological analyses were not performed. [23]

Coronary vasculitis can occur as an isolated entity or as a manifestation of a systemic disease, i.e. Churg–Strauss syndrome, systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis or Behçet's disease.[24-26] Mixed inflammatory infiltrate, rich in eosinophils was described in many cases of coronary artery dissection thought without exact understanding of the mechanism[27, 28] except while occurring as a consequence of instrumentation of the coronary arteries. Coronary artery dissection was largely described in young women, with many cases occurring in the early postpartum period [29]. Eosinophilic coronary periarteritis was recently reported by Kajihara *et al* as a new type of coronary arteritis, in which the patients present with Prinzmetal's vasospastic angina, eosinophilic inflammation limited to the adventitia (primarily in the LAD artery) and the absence of other types of vasculitis. An allergic or immune-mediated mechanism was suggested to play an important role in the presence of eosinophilic inflammation around the vasa-vasorum of the coronary arteries. [30] A similar case was presented by Takira *et al,* who suggested that marked inflammation with eosinophils in the adventitia causes intimal thickening and vasospasm of the coronary artery via cytokines and lipid mediators [31]. Eosinophils and hypersensitivity coronary syndrome (aka Kounis syndrome) has also been described as three clinical variants: vasospastic allergic angina, allergic myocardial infarction and stent thrombosis with the occluding thrombus infiltrated by eosinophils and/or mast cells. [32, 33] It is fairly common to observe macrophages in areas of ruptured plaques, but only recently has been suggested that eosinophils might play an important role in the development of

coronary atherosclerosis.[34, 35] These mechanisms may be involved in the present case considering the eosinophilic infiltrations seen on histological examination. The tryptase measurement, useful in the post-mortem diagnosis of anaphylaxis and anaphylactoid reactions as its blood level rise from a few minutes up to several hours after mast cell degranulation [36], was in the "normal" range. In our opinion the postmortem tryptase level in this case does not exclude a hypersensitivity coronary syndrome considering that tryptase level is not consistently elevated in drug-induced anaphylaxis. [37, 38]The toxicological analyses confirmed both chronic and acute cocaine abuse, as well as the presence of levamisole. Levamisole is a highly toxic substance known to provoke hypersensitivity reactions. Levamisole increases T-cell activation and proliferation, neutrophil mobility, adherence, and chemotaxis and increases the formation of antibody to antigen complexes. [7, 9, 39] Phenacetin, found in the pericardial fluid, is another recognized cocaine adulterant, but its reported health consequences have been linked to renal failure and carcinogenicity.[4] In our opinion, the eosinophilic inflammation of the coronary artery and the acute coronary syndrome could be related at least partly to levamisole use although it is impossible to separate the complications resulting from cocaine and/or levamisole use.

It is very important to document and report all possible manifestations of adultered cocaine abuse in order to avoid any clinical misdiagnoses and to prevent unnecessary treatments with potentially toxic therapies. [4, 5, 8, 12] This is the first post-mortem case report of eosinophilic inflammatory coronary artery pathology following levamisole

adultered cocaine abuse, complete with post-mortem imaging and toxicological analyses. The coronary pathology and sudden death in this case can be considered as possible levamisole-adultered induced complication, which have not been previously described although it is impossible to prove that levamisol played any role in the disease process. The rise in cocaine addiction worldwide and the increased use of levamisole adulterated cocaine underscores the clinical and public health needs to fully understand the effects of adultered cocaine abuse on the cardiovascular system.

Figures

Fig.1 Axial image of the arterial phase of MPMCTA (a) showing pulmonary edema with bilateral pleural effusion (yellow arrows in a), as well as pathological enhancement of the myocardium of the left ventricle and septum (red arrows in a) related to an old infarct. 3D-reconstruction of the coronary arteries (b) obtained after the arterial phase of MPMCA clearly demonstrates a perfusion problem of the proximal segment of the LAD artery, corresponding to a luminal stenosis (arrow in b). Autopsy revealed a small eroded plaque in the proximal portion of the LAD (arrow in c) and healed transmural infarcts in the antero-lateral wall of

the left ventricle (white arrow in d) and in the anterior part of the septum (black arrow in d)

Fig. 2 Histological examination of the proximal LAD artery showing eosinophilic infiltrates within the adventitia (a), and the intima (b) and the initial thrombotic phenomena (b, c, d) Hematoxyline & Eosin stain

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Figure(s)

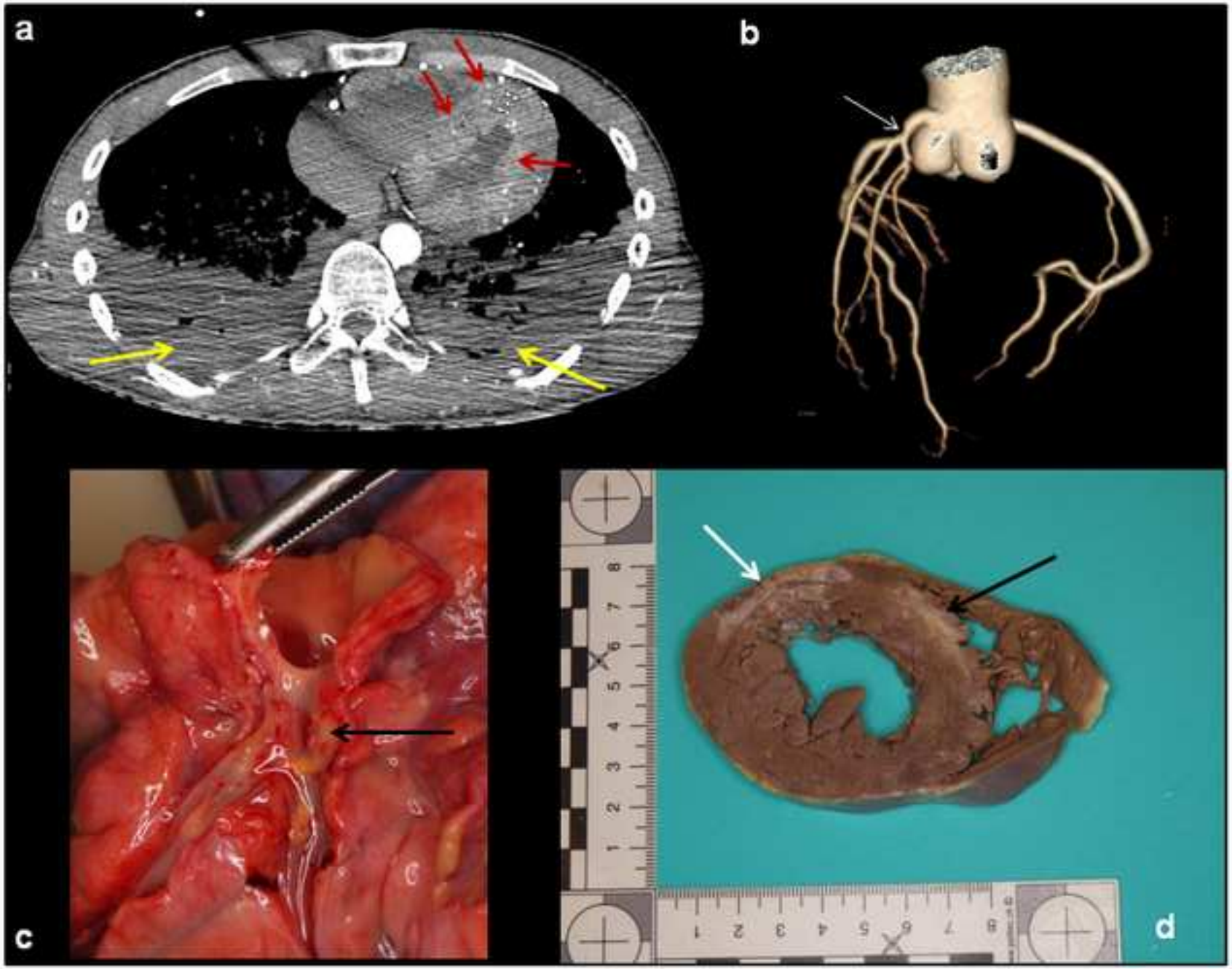

Fig. 1

Figure(s)

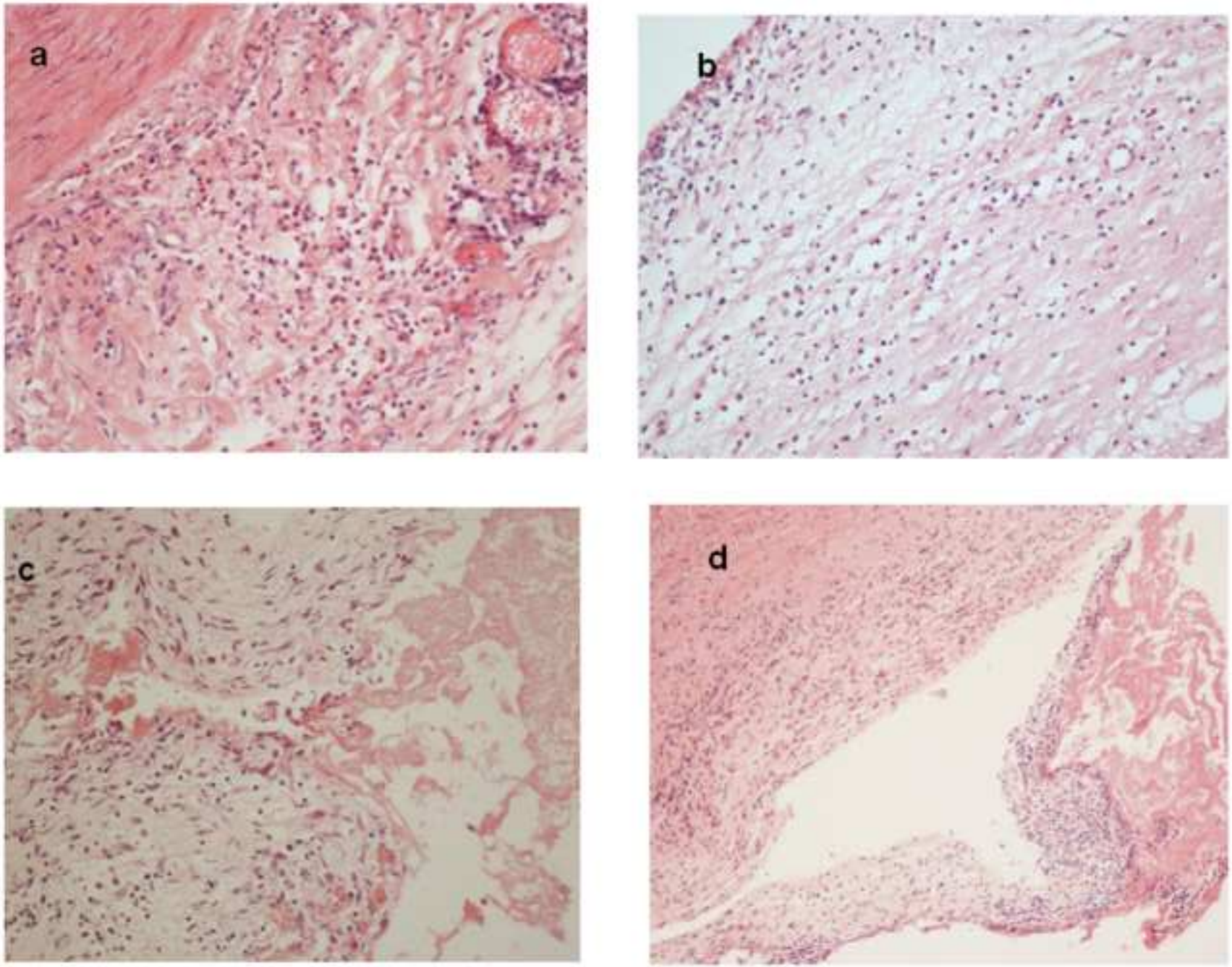

Fig. 2

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