Widespread septic embolization in injection drug use mitro-aortic infective endocarditis as a remote cause of death

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Abstract

Injection drug use-related infective endocarditis (IDU-IE) assumes peculiar epidemiological, pathogenetic, and prognostic characteristics that allow to consider it a distinct nosological entity, as well as a current problem of considerable social weight. Incidence is reasonably underestimated because diagnosis is often accidental in postmortem examination when drug-related death is suspected. In many cases, postmortem toxicological examinations are negative for acute drug abuse, and findings of infective endocarditis became relevant in the explanation of the mechanism of death. Extracardiac involvement of infective endocarditis is rarely reported as fatal. Fragmentation and embolization of bacterial vegetations can be associated with parenchymal infarcts, systemic spread of the infectious process by formation of an abscess. A case of septic shock as a consequence of the constant bacteremia determined by the continuous proliferation and release of bacteria into the circulation is presented in an injection drug user with left-sided endocarditis and widespread septic embolization. Authors reviewed forensic and medical literature and promote epidemiological value of medical and forensic autopsy. Extracardiac involvement of infective endocarditis may represent a remote and alternative cause of death in injection drug users, and an early diagnosis can be relevant for prognosis. Postmortem examination still represents a valuable opportunity of learning for clinicians and improving diagnostic accuracy with injection drug users. A call for changing of attitudes and practice toward autopsy is finally demanded.

Keywords Injection drug use infective endocarditis · Unexpected death · Widespread septic embolization · Educational autopsy

Introduction

Infectious endocarditis (IE) is a severe heart affection mainly involving cardiac valves, characterized by a high rate of mortality. The penetration of microorganisms from various districts (airways, skin, urogenital, and digestive system) or the outside of the body into the bloodstream makes bacterial colonization of heart valves possible, especially in the presence of preexisting endocardial defects or prosthetic material. Injection drugs use (IDU)—commonly performed in nonoptimal hygienic conditions—can, on the one hand, inoculate the microorganisms into the blood stream and, on the other hand, favor damage to vascular structures. For these reasons, IDU is considered an important predisposing factor for the development of IE and represents one of Dukes' minor criteria in the diagnosis of this disease [1]. Moreover, injection drug use-related IE (IDU-IE) assumes peculiar epidemiological, pathogenetic, and prognostic characteristics that allow to consider it a distinct nosological entity, as well as a current problem of considerable social weight. In fact, developed countries are experiencing a new significant increase in IDU consisting of an opioid endemic; this phenomenon is extensively known and described in the USA, where a raise in consumption is supported by a widespread prescriptive inadequacy of pain medication [2–5]. Because of the emergence of this socio-health scenario, IDU-IE and other IDU-related conditions prevalence are becoming a raising and challenging issue, especially in the young population [6, 7]. Autopsy in suspected drug-related death could help to improve diagnostic accuracy in population at risk of infective endocarditis and to prevent fatalities. The present study proposes a particular case of lethal double-valve IDU-IE with widespread microembolization diagnosed during clinical autopsy. The subsequent review of the most recent available scientific literature, supported by the

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experience acquired in the field of autoptic practice, has the aim of highlighting some relevant pathophysiological aspects of IDU-IE for use in preventive politics, clinical setting, and postmortem investigation.

Case report

A 47-year-old man was admitted to the Emergency Department in absence of vital signs. Advanced resuscitation maneuvers were unsuccessful. In the history, recurrent fever was reported in the last weeks up to 39 °C. In the morning, few hours before cardiac arrest, body temperature was 38.1 °C. Other pathological conditions were excluded by the relatives. Moreover, a history of intravenous heroin use was reported, and then, prosecutor office was alerted. A complete autopsy was performed 2 days after death. External examination was negative, and injection sites were excluded. Mild cerebral edema was recorded. The heart was normal in shape, size (12 × 11 × 4.5 cm), and weight (380 g). Coronary vessels were normal without significant occlusion of the lumen. Gross examination of the heart was performed according to in-flow/out-flow method. Volume of atrial and ventricular chambers was normal as well as thickness of myocardial walls of the left and right ventricles. A soft consistency and mildly hemorrhagic vegetation, 1.5 × 1.8 × 1.6 cm in size, was observed on the anterior cusp of mitral valve (Fig. 1). A second hard consistency vegetation, 0.8 × 1.2 × 0.5 cm in size, affected the line of closure of the ventricular surface of the aortic valve (Fig. 2). Pulmonary edema with white foam from the main bronchi was also detected. The liver was increased in size and weight (2450 g), with hard consistency and granular aspect of cutting surfaces. Splenomegaly was recorded. Other organs were unremarkable for noteworthy alterations. The immunoassay toxicological screening test performed on urine and blood specimens in order to define the presence of the most frequent substances of abuse was negative. This result was subsequently confirmed by the GC-MS evaluation. At histological

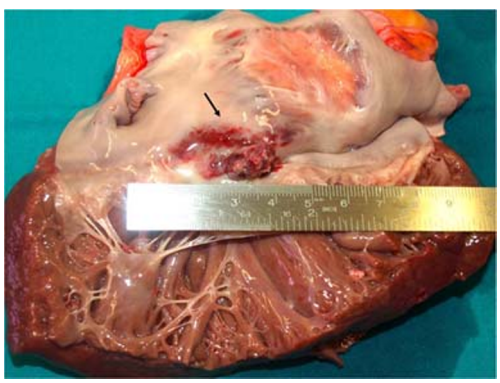

Fig. 1 The anterior cusp of the mitral valve affected by a soft consistency vegetation with endocardial perivalvular hemorrhagic infiltration (black arrow)

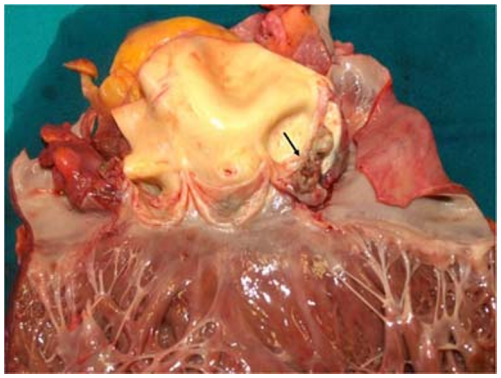

Fig. 2 Vegetation allocated on the line of closure of the ventricular surface of the aortic valve (black arrow)

examination, vegetations appeared as an abundant fibrinous material containing basophilic bacteria colonies and polymorphonuclear leukocytes (Fig. 3a–b). Microcolonies of gram-positive bacteria stained with PAS and Giemsa were also detected (Fig. 3c–d). Widespread septic embolization in the brain, heart, liver, spleen, and kidney was observed with basophilic bacteria colonies stained with PAS and Giemsa (Fig. 4a–d). Septic shock as a consequence of the constant bacteremia determined by the continuous proliferation and release of bacteria into the circulation in an injection drug user with left-sided endocarditis and widespread septic embolization was indicated as the cause of death.

Discussion

IDU-IE is classically described as a pathology affecting right valves of the heart, in view of the most recognizable predisposing factor consisting in the inoculation of microorganisms—localized on the skin surface, on infected needles, or inside the injected substances—into the blood stream and their consequent migration to the right side of the heart [8]. Under the epidemiological point of view, many population-based studies show a general increase in the incidence of IE and, more markedly, of IDU-IE, over the last few years [9–11]. IDU-IE is predominately ascertained in male, young, and white subjects, with small differences among studied populations [12]. A retrospective study conducted on the population of Pennsylvania showed a marked increase in the diagnosed cases of IDU-IE in the period 2013–2017, confirming a predominance of cases in male subjects (53% of overall IDU-IE cases) [13]. The same study highlighted a median age of IDU-IE patients of 33 years with interquartile range (IQR) of 27–45, against a median age of 69 years and a wider age distribution (IQR, 56–80) in the group of non-IDU-IE patients. IDU is considered the main predisposing factor for IE in the young population; in this regard, it is reported that approximately 90% of IE in the 15- to 34-year-old population have an association with injection drug use [6]. The incidence of IE within the population of injection

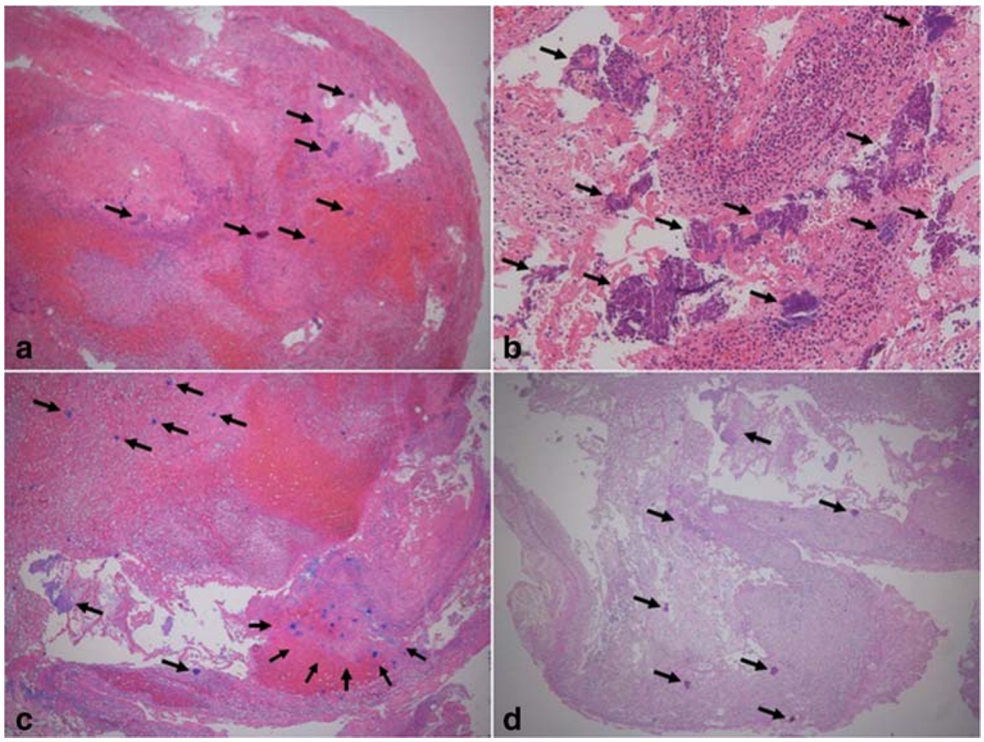

Fig. 3 Low magnification of a vegetation of the mitral valve. Vegetation appears as an abundant fibrinous material containing basophilic bacteria colonies (black arrows) and polymorphonuclear leukocytes (**a**–**b**). Microcolonies of gram-positive bacteria (black arrows) stained with PAS (**c**) and Giemsa (**d**)

drug users is estimated to be between 1.5 and 3.3 cases per 1000 subjects per year. White young males belonging to lowest socioeconomic classes are most affected with chronic comorbidities. Admission rate of 27% for infective endocarditis in intravenous drug abuser aged < 30 years old was reported from the Centers for Disease Control and Prevention. People who inject drug are generally described as likely to leave the hospital against medical advice and recurrence rate of infective endocarditis is higher than nonuser population [14]. Infective endocarditis in people who inject drug, is generally related with *Staphylococcus aureus*. Fungal infective endocarditis is less frequent and with a prevalence for *Candida* species followed

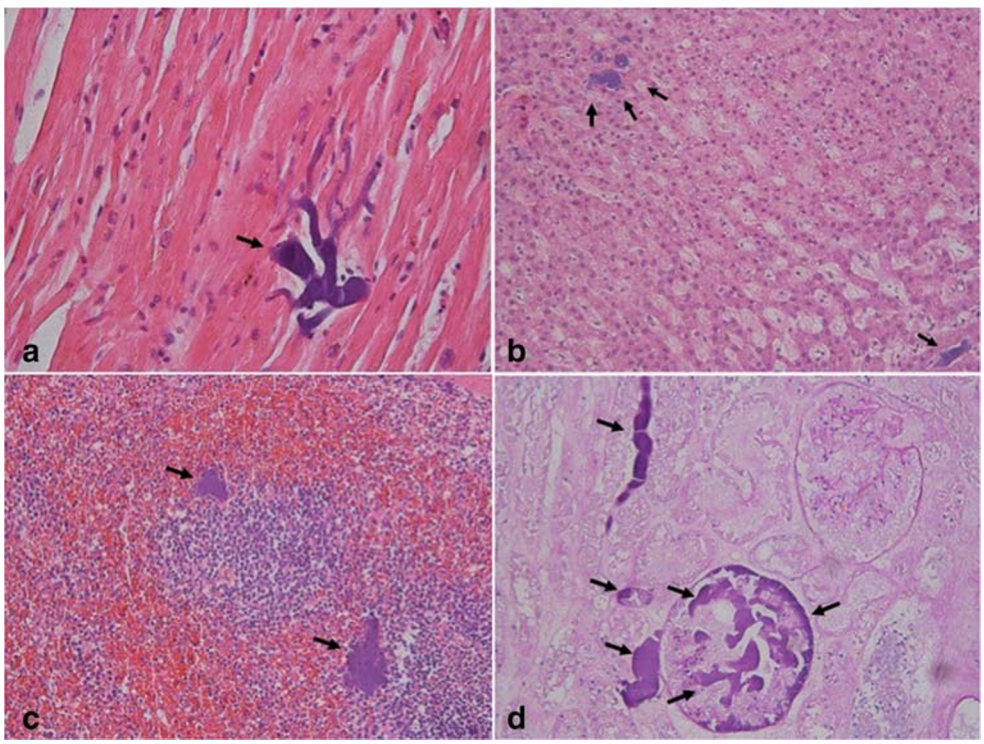

Fig. 4 Widespread septic microembolization (black arrows) in the heart (**a**), liver (**b**), spleen (**c**), and kidney (**d**)

by *Aspergillus* [15]. The attachment of microorganisms to valve surfaces, the following production of biofilm, and the development of a bacterial vegetation usually require the presence of predisposing factors, such as the preexistence of a valve defect. Moreover, even if it is widely shared in the scientific community that a large majority of endocarditis affecting right heart valves is to be referred to an IDU, international literature does not provide certainties about the right-left valves distribution of bacterial vegetations in course of IDU-IE, which frequently affect left valves [16–18]. Many possible roles of injection drugs in damaging heart valves have been hypothesized, including the toxicity exerted by solvents or the injected drug itself as well as the hemodynamic modifications determined on the systemic and pulmonary circulation (e.g., the increase in afterload in cocaine and amphetamines, increase in pulmonary pressure in heroin) [19]. A direct role on the immunoregulatory mechanisms can be played by the injected substance; in this regard, it is widely recognized that opioids are able to interfere with some pathways involved in the mechanisms of inflammation, causing changes in the release of cytokines responsible for immunosuppression (IL-10) or in the activation of inflammation (IL-12, IL-15, TNF-α, and COX-2); even if many studies suggest a potentially immunosuppressive effect of opioids, increase in pro-inflammatory mediators is particularly described in central nervous system and seems to be associated with hypoxic-ischemic phenomena [20, 21]. Finally, the higher prevalence of HIV (and HCV) in IDU patients rather than in general population is responsible of a wide immunocompromised condition and the possibility of more frequent and severe infective diseases in the considered population. The assumption of these pathogenetic mechanisms allows to explain the possible localization of IDU-IE vegetations also in left valves. Prognosis of intravenous drug users with infective endocarditis is poor, even after surgery [22–24]. A twofold increase in infective endocarditis deaths among < 35 years old drug abuser has been reported with all cause of infective endocarditis mortality [25]. Factors associated with higher mortality in people who inject drug are not completely understood. Age, site of infection, and lack of in-hospital care are proposed as affecting mortality rates. The high mortality rate of infectious endocarditis is supported by multiple pathogenetic mechanisms that can be expressed both at cardiac and extracardiac level. Cardiac involvement can directly result from the destructive action of the infectious process on the valvular structure, able to determine cusps perforation, rupture of tendinous cords, and consequent cardiac failure [26, 27]. Left-sided infection and bilateral infection are associated with mortality rates higher than right-sided endocarditis [28]. When a drug abuse-related death is suspected, autopsy is mandatory, and a complete toxicological investigation is needed to exclude acute intoxication. Gross examination of fixed in formalin heart may be helpful in a detailed description of cardiac pathological findings. In case of IDU-EI, vegetations may widely differ in size and diameter and are generally located on the atrial aspect of the mitral valve and on the ventricular aspect of the semilunar. The extension of the infection outside the valve structure can lead to the formation of abscesses or fistula which, depending on the location, can even determine conduction alterations or predispose to heart rupture. Moreover, if the vegetation is large, sudden death due to complete occlusion of valve lumen is possible [29]. Valvular vegetations are generally composed of a matrix of fibrin and platelets with macrophages and bacterial microcolonies infiltrate by polymorphonuclear cells. Extracardiac involvement can occur, at first, for fragmentation and embolization of bacterial vegetations, which is more frequently observed in the case of left-sided infective endocarditis. Most affected organs from septic embolism in the setting of infective endocarditis include central nervous system, extremities, spleen, and kidney. Coronary vessels, iliac and mesenteric arteries, liver, and the lung are less commonly affected [30]. The organ damage deriving from embolization consists in parenchymal infarcts and, in the case of septic embolization, in the possibility of spread of the infectious process by formation of an abscess or a mycotic aneurysm in affected arteries [31–33]. Embolization in the central nervous system with intracranial mycotic aneurysm and splenic infarction often complicates left-sided endocarditis. When pulmonary septic embolization occurs with systemic manifestations, bilateral endocarditis or paradoxical embolism should be considered [34]. In cases of disseminated septic embolization, medical management becomes a challenge, and prognosis is poor. Also, the constant bacteremia determined by the continuous proliferation and release of bacteria into the circulation leads to the possibility of development of sepsis and septic shock and causes the hyperstimulation of immune system through the activation of both humoral and cellular pathways [35]. For this reason, signs of splenomegaly and hypergammaglobulinemia are frequently observed at autopsy, and the possible formation and deposition of immunocomplexes and complement components in various tissues are related to multiple immunological issues such as the appearance of systemic vasculitic phenomena and glomerulonephritis which, on the other hand, have complex and partially unknown mechanisms [36, 37]. Given the wide immune system activation, studies on inflammation markers revealed a possible role of cytokines as diagnostic and prognostic evaluation tools. In fact, IL-1β, IL-6, IL-8, IL-10, IL-12, and TNF-α are significantly higher in patients with IE compared to healthy subjects and are especially expressed in patients with fever and other systemic symptoms [38]. Moreover, patients with a poor outcome are interestingly characterized by higher levels of IL-6, IL-8, and IL-10. Inflammatory modulation also seems to be involved in the poor postsurgical outcome of IE, as demonstrated by the inadequate activation of the inflammatory system—able to enhance the occurrence of complications—in response to heart surgery procedures [39].

Conclusion

IE should be suspected in all the cases of recurrent fever of unknown origin. However, the scarce specificity of the presented symptomatology rarely directs the nonspecialist physician toward a correct diagnostic procedure (echo, blood culture) for identifying IE [40]. In the case of IDU-IE, the formulation of a correct diagnostic suspicion can be even more complex. In fact, IDU is an anamnestic notion little investigated by the doctor and usually not reported or even hidden by the patient; in addition, it must be considered that IDU patients are particularly reluctant to medical evaluations, due to the social stigma that a substance addiction usually determines. For this reason, the detection of infectious endocarditis can be delayed up to the advanced stages of functional impairment or, as in the present case, during postmortem examination; the use of a nontargeted antibiotic therapy, on the other hand, is associated with the only reduction of symptoms (and possible negativity of blood cultures) which can emphasize the aspecificity of clinical characteristics and contribute to the development of drug resistance mechanisms, with all the medical and social-related issues. Moreover, the higher recurrence rate compared with non-IDU-related endocarditis must be considered; this aspect has a considerable importance not only as a prognostic factor but also in the correct therapeutic planning. In fact, the recurrence of IE after intervention—usually related to the persistence of an injection drugs abuse—determines high readmission rate and a poor long-term postsurgical outcome. For these reasons, evidences suggest that intervention should be considered, in particular for right-sided IDU-IE, only in case of important functional impairment, recurrent or persistent complications, or infection by particularly antibiotics-resistant microorganisms (e.g., fungi); otherwise, pharmacological therapy is suggested. From this point of view, much could be done, through the multidisciplinary treatment of the underlying abuse condition, in order to avoid the recurrence of episodes and improve prognostic aspects. The latter, in fact, have a vast room for improvement, in consideration of the epidemiological characteristics of the IDU-IE [41–43]. Prompt identification of the condition, at contrary, allows the planning of targeted and less invasive therapy that should be comprehensive of the treatment of both IE and substance addiction in order to prevent the appearance of recurrences or other IDU-associated conditions [44]. Decline of autopsies is observed in the last 50 years. Attempts to reduce healthcare costs and concerns about litigation and cultural aversion to interfering with cadavers are cited as main reasons for low autopsy rates worldwide. Medical overconfidence with diagnostic and therapeutic capacities is often recorded after autopsies, with a rate of misdiagnoses and diagnostic mistakes unchanged over time. Postmortem studies revealed that incidence of infective endocarditis in drug abusers is generally underestimated, and its main role in unexpected death is far to be completely known. Widespread septic embolism in left-sided IDU-IE is a remote cause of death and needs a rigid protocol of macroscopic and microscopic investigations to be confirmed. Autopsy still represents an opportunity of learning for clinicians and improving diagnostic accuracy and prognosis in injection drug users [45].

Authors' contributions All the authors contributed equally to the conception and design of the study, acquisition of data, or analysis and interpretation of data; drafted and revised the article critically for important intellectual content; and approved the final version before its submission.

Availability of data and material The authors confirm that the data supporting the findings of this study are available within the article and supplementary material (pictures, toxicological investigations, etc.) are available from the corresponding author upon request.

Compliance with ethical standards

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

Informed consent Informed consent was obtained from the family of the deceased for the publication of his information and imaging.

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