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Midzonal lesions in yellow fever: A specific pattern of liver injury caused by direct virus action and in situ inflammatory response

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Summary Yellow fever is an acute infectious, non-contagious disease characterized by intense vasculopathy and lesions in different organs. In the liver, one of the main targets of the virus, the infection induces a characteristic midzonal injury characterized by hepatocyte necrosis, apoptosis and steatosis. This characteristics pattern of liver injury in yellow fever is also observed in conditions of low-flow hypoxia and other infections such as dengue and Rift Valley fever. There are no reports in the literature explaining the genesis of this peculiar histopathological pattern in yellow fever. Some hypotheses have been proposed to explain the mechanism of this midzonal distribution pattern observed in the liver such as low-flow hypoxia and tropism of the virus toward hepatocytes in this area. These hypotheses are discussed in view of more recent findings regarding the pathogenesis of yellow fever and regarding hepatic physiopathology, and a new hypothesis is proposed: the midzonal necrosis is consequence of action of combined factors mainly the direct cytopathic effect of YFV associated with a potent immune response in which CD4+ and CD8+ lymphocytes and the cytokines, especially TGF-β, but also TNF-α and IFN-γ play an important role.

Introduction

Classically, the pattern of host–parasite interaction is a determinant factor of cell injury and essential in the progression and prognosis of infectious and parasitic diseases. In hepatic viral infections, the resulting lesions are generally not only the product of interactions between the infectious agent and host cell, but are also due to factors inherent to systemic alterations, with important secondary involvement of the liver [1]. Viral hemorrhagic fevers such as yellow fever, dengue and Rift Valley fever present as severe acute febrile syndromes, with hemorrhagic phenomena being their most prominent manifestations due to the effects of infection on the endothelial cell [1,2]. Some of these infections frequently share a

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common histopathological substrate, a fact leading to cellular alterations that are found in more than one of theses diseases such as apoptosis observed in yellow fever and dengue [2].

Regarding yellow fever, like in other viral hemorrhagic fevers, the hepatic involvement is characterized by intense injury to the midzonal area, with hepatocyte steatosis, apoptosis and necrosis. Several studies have been conducted in an attempt to elucidate the etiopathogenic mechanisms underlying the infection with yellow fever virus; however, some questions continue to be extremely controversial and the hypotheses raised require experiments for their final objective confirmation [2,3]. Among these aspects, the preferential midzonal injury has gained interest because several data indicate the presence of distinct mechanisms for the genesis of these characteristic lesions. The pattern of midzonal hepatic injury has been described for different pathological conditions including states of hypoxia and viral infections such as yellow fever, dengue and Rift Valley fever [2,4]. Several hypotheses have been proposed to explain this preferential lesional pattern, including viral tropism, immune response activation and low-flow hypoxia-induced injury. Although characteristic, the intensity of midzonal injury varies among the different diseases and yellow fever is a model of viral infection in which this peculiar aspect of the liver represents a marked feature.

The existent hypothesis

The pattern of midzonal injury is a characteristic histopathological finding of yellow fever when considered together with the other alterations that are observed in the liver during the course of infection. On the other hand, the same characteristic pattern is observed with relative frequency in infections induced by other viral hemorrhagic fevers such as dengue and Rift Valley fever viruses. Therefore, two hypotheses have been raised to explain the occurrence of this characteristic pattern. The first hypothesis proposes that midzonal injury is the consequence of preferential tropism of the virus toward hepatocytes in the midzone region, inducing greater injury in this region compared to the other regions of the hepatic lobule due to the effect of the virus on the cell and the action of cellular immune factors and cytokines able to induce cell death of infected hepatocytes. The second hypothesis suggests the possibility that the characteristic midzonal pattern of hepatic injury is the result of low-flow hypoxia as a consequence of marked alterations in endothelial cells, associated with a greater susceptibility of midzonal hepatocytes to states of low oxygen concentration.

Evaluation of the hypotheses

The classical studies of Councilman [5] have originally described the main histopathological alterations observed in yellow fever liver, which were later complemented by Rocha-Lima in 1912 [6]. In these studies, the authors identified steatosis and hyaline degeneration as characteristic alterations of yellow fever when associated with a peculiar topographic pattern of more intense midzone distribution [6,7]. In subsequent studies, Rocha-Lima emphasized the importance of this histopathological picture of midzonal injury for the diagnosis of yellow fever and regarded it as a feature of this disease. Other authors later confirmed these findings [7–9].

Recent studies have demonstrated that the anatomopathological aspects of the liver in yellow fever are characterized by the severity of the lesions throughout the lobule. However, the samples were characterized by a clear preferential involvement of zone 2 (midzonal area), permitting the identification of narrow bands of preserved hepatocytes around portal spaces and the centrolobular vein. Semiquantitative investigations showed that the centrolobular and the midzone regions are, in terms of the degree and extent of involvement the most affected areas, with a greater preservation being observed for zone 1. As also shown in other classical studies, this latter zone generally maintains a narrow band of preserved hepatocytes around the portal space, showing variable degrees of degenerative and regenerative alterations [7].

Despite the large number of studies reporting this selective predisposition for zone 2 in liver lesions of yellow fever, any adequate explanation for this particular type of involvement have not been described. On the other hand, later studies [10] have demonstrated diversity in different acinar regions of the liver, characterizing the biochemical and ultrastructural heterogeneity of the hepatic parenchyma and its susceptibility to lesions induced by systemic conditions of ischemia and hypoxia which, to some extent, may explain the presence of selective lesions during the course of yellow fever or other infections and also other situations of impairment of blood flow to the liver [4,11].

It should be added that the studies published by De la Monte et al. [4] and Suematsu et al. [11] have