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Editorial

Pathology of infectious diseases: new agents, opportunistic, neglectable, emergent, reemergent diseases and why not super resistant nosocomial bacteria?

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We are living in a world with constant social, economic, and demographic change: rapid mobility of a large contingent of people over long distances in the short period of time; social imbalance; populations deprived of liberty and refugees; poor vaccine coverage; and changes in the climate and ecosystems that favor vector proliferation and circulation of agents (mainly viral) are some examples of factors that interact as a puzzle to explain the variety of epidemics that have been experienced in recent years worldwide.[1]

In Brazil, we have been in the midst of a hurricane of emerging and re-emerging disease epidemics over the past 35 to 40 years, especially in the last 4 to 5 years, which was worthy of an editorial in the *New England Journal of Medicine*, entitled "... Once Again on the Radar Screen ... "[2] Examples include AIDS, dengue, leptospirosis, rubella, and measles in the 1980s and 1990s; dengue and H1N1 in the 2000s; annual dengue epidemics and the emergence of Chikungunya and Zika from 2014 to 2019; and the re-emergence of yellow fever, respiratory syncytial virus and measles from 2017 to 2019 (Figure 1).

In addition, in recent years, we have seen the resurgence of sexually transmitted diseases, such as HIV infection among young people; syphilis, with a large number of maternal-fetal cases; and sexually transmitted hepatitis A and B—not forgetting tuberculosis and leprosy, which are far from being considered eradicated or under low endemic levels.

This whole scenario makes the pathology of infectious diseases important, not only in Brazil, but worldwide. For instance, in the case of Zika, it was essential to understand the disease early in the epidemic through the autopsy case report of a conceptus with microcephaly, whose mother acquired the disease in northeastern Brazil. It was possible to describe macroscopy and microscopy of the brain in detail, to observe the agent by immunofluorescence and electron microscopy in the lesions, and to sequence the viral strain obtained in the brain tissue, determining its phylogeny.[3] Subsequently, works by Chimelli et al.[4] and Martines et al.[5] demonstrated that the Zika virus can produce a myriad of lesions in the central and peripheral nervous system due to a change in neuronal development, maturation, and migration, as well as lesions in the maternal placenta. The amount of research accumulated in Zika since the beginning of the epidemic is huge, and the pathology of infectious diseases plays a decisive role. More recently, during the yellow fever epidemic in Brazil from 2017 to 2019, previous and current pathology studies have allowed a better understanding of the pathogenesis of the disease.[6-9] In our region, where hemorrhagic fevers are endemic (e.g., dengue, leptospirosis, spotted fever, hantavirus, sepsis), the emergence of yellow fever has

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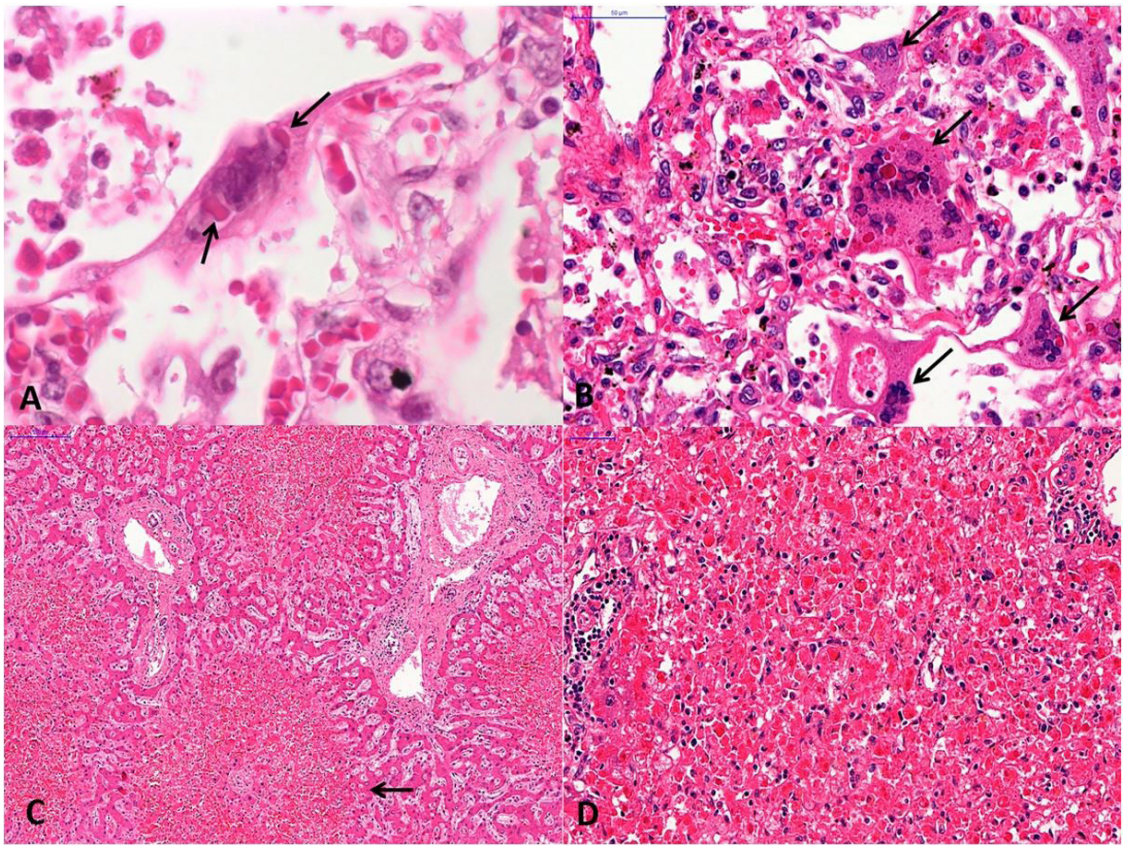

Figure 1. Pathology of viral infection. **A –** Fatal respiratory syncytial virus pneumonia in an infant. The arrows show a polykariotic infected pulmonary epithelial cell, with eosinophilic rounded cytoplasmic inclusion; **B –** Fatal Measles pneumonia (Hecht pneumonia) in a child under treatment for non-Hodgkin lymphoma. The arrows show multinucleated giant cells (Warthin-Finkeldey cells), with nuclear and cytoplasmic eosinophilic inclusions; **C –** Fatal dengue shock syndrome, with the typical mid-zonal hepatitis (arrow), with more preserved hepatocytes near to periportal area. The inflammatory tissue reaction is mild; **D –** The liver in a case with fulminant yellow fever. Similar to severe dengue, there is a mid-zonal hepatitis with numerous steatotic and apoptotic hepatocytes. The inflammatory reaction is also mild, with mononuclear infiltrate mainly located in the portal tracts. H&E stain. *Magnification.* **A, B –** 400x, **C –**100x, **D –** 300x.

become a problem for clinicians and epidemiologists. The pathologist's action is decisive for the definition and exclusion of suspected cases, especially fatal ones, allowing accurate knowledge of the mortality rate and the magnitude of the problem.

What about super-resistant bacteria? In general, the literature describes the pathology caused by pyogenic bacteria, whether gram-positive cocci or gram-negative bacilli, as a suppurative inflammatory process, which is indistinguishable between agents regardless of antimicrobial susceptibility profiles.[10] In particular, I disagree with this point of view, at least partially. Little is known about the pathology of multidrug-resistant bacteria, and studies—even case reports—are extremely welcome as is Larry Nichols' report *Death from pan-resistant superbug*, in this issue of *Autopsy & Case Reports*, describing the autopsy of a α-1-antitrypsin deficient patient who was a chronic corticosteroid user and developed fatal pneumonia caused by *Acinetobacter baumannii* resistant to all tested antibiotics.[11] The description of the pathology of multi-resistant pyogenic agents may raise relevant insights for understanding the pathogenesis of infection and the virulence of an agent. For example, *Pseudomonas aeruginosa*, is a gram-negative bacillus, which causes pyogenic infection, with a particular vascular tropism inducing coagulative vessel necrosis and ischemic tissue damage.[12]

In the case described by Nichols, I am struck by the predominantly macrophage inflammatory response

with a large number of bacteria phagocytized by alveolar macrophages (Figure 2 of the article). Some hypotheses may arise for this morphological scenario, which may be answered in the future by controlled experimental studies: is the macrophage response effective in destroying *A. baumannii*? Are the macrophages present type M1 or M2? Are the neutrophil response, complement, and antibodies compromised? It should be considered that the patient was a chronic user of corticosteroids. However, are there particularities in *A. baumannii* virulence? Some of these pathogenetic responses, if answered, may allow the discovery of new therapies. Therefore, the relevance of a detailed description of the pathology of multi-resistant superbugs. As a note, some autopsies of *A. baumannii* pneumonia recently performed by *Departamento de Patologia – Faculdade de Medicina da Universidade de São Paulo* (*personal observation, unpublished data*), present the same morphological findings as described by Nichols. Of course, detailed pathology studies with larger numbers of resistant bacteria with different phenotypic susceptibility patterns would provide more information on pathogenesis. Perhaps it would only be possible through the interaction between different health centers around the world.

The history of the pathology of infectious diseases coincides with the history of general pathology and modern medicine itself. From the earliest descriptions of the pathology of tuberculosis and yellow fever to the discovery of AIDS[13-15]; the Ebola epidemic in the 1990s[16]; the *Bacillus anthracis* bioterrorism attack in the early 2000s[17]; the epidemics of SARS and pandemic influenza throughout the 2000s[18,19]; and more recently the Zika epidemic,[3-5] with congenital syndrome, the pathology of infectious diseases plays a decisive role in understanding the pathogenesis of an infectious agent. Moreover, the pathology of infectious diseases is part of preparedness in case of an epidemic, as it defines or excludes the diagnosis of a disease. With this medical and social function, the pathology of infectious diseases can reach the fullness of its importance with the autopsy, when the pathologist examines all organs of a fatal case, allowing him/her to determine the mechanism of transmission, the mechanism of injury through the involvement of all organ systems, and to determine the cause of death. Of equal importance, the pathologist can characterize the individual's in situ immune response, and predict the prognosis of an infectious disease and the therapeutic response by analyzing tissue damage.[20-22]

The arsenal of methodologies used by the pathologist for diagnosing infectious disease is mostly based on classic, low-cost techniques that require familiarity and expertise with the morphological aspect of the agents to complete their report: hematoxylin and eosin, and special stains such as Grocott, Ziehl-Neelsen, period acid-Schiff, Mucicarmine, Giemsa, and others.[23] Added to them is indispensable electron microscopy (EM). Perhaps it is in the field of infectious diseases where the great importance of EM still lies, and it is worth maintaining the technique and art of this old ancillary method. EM can elucidate difficult cases by discovering the etiology of a disease (especially viruses), in glutaraldehyde-fixed or paraffin-embedded tissues during epidemics, where immunohistochemistry antibodies or polymerase chain reaction (PCR) primers are not yet available.[24] Molecular biology techniques such as in situ hybridization, PCR and gene sequencing—including next generation sequencing—are new methods that can be used with frozen or fixed tissues; however, these techniques are not always available in resource-poor regions (Figure 2).[25]

The expert in infectious disease pathology can act beyond the autopsy and analysis of surgical specimens (biopsies, cytology). The pathologist can assist research groups in evaluating the pathology of experimental models of infectious diseases and, within the new concept of "one health," interact with veterinarians, environmentalists, and epidemiologists in epidemic situations or in comparative pathology studies of zoonoses (e.g., leptospirosis, yellow fever, spotty fever, west Nile, etc.).[26]

Considering all that has been commented on previously regarding the importance of the pathology of tropical infectious diseases, a recent review article, written by Hofman et al.,[25] points out that this specialty needs to grow all over the world, stimulating the formation of young pathologists with expertise in this field. To reach this aim, stimulus must be created to attract resources to include new diagnostic methodologies in the field and to establish research, education, and patient-care networks, where specialists from different regions of the world can be connected to exchange knowledge.[25]

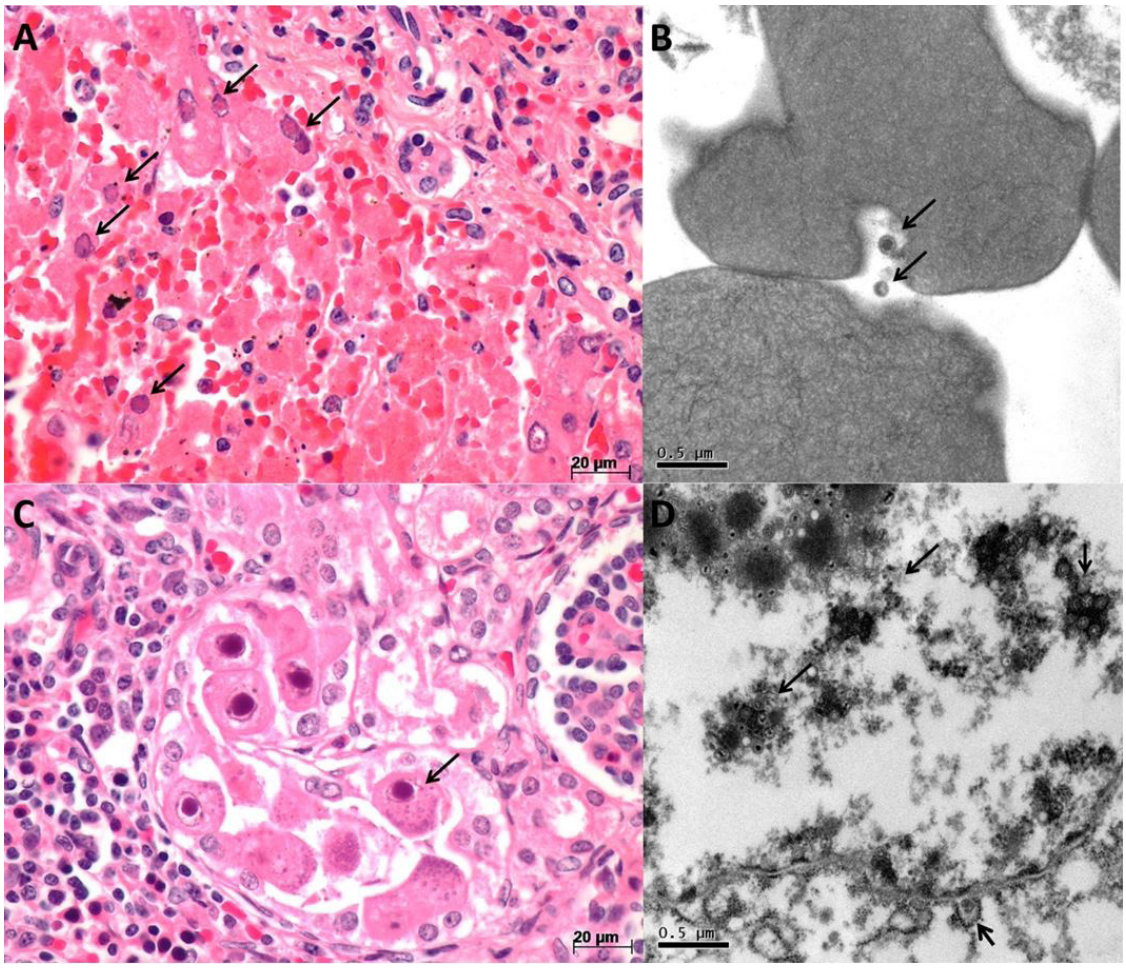

Figure 2. Pathology of Herpes virus. **A, B –** Fulminant HSV1-hepatitis in a patient with X-linked agammaglobulinemia. The H&E stained slide (A) shows numerous necrotic hepatocytes and some (arrows) with typical Cowdry type A inclusion (nuclei with ground glass appearance and multinucleated cells with nuclear molding and peripheral margination of chromatin). The electron microscopy (B) shows HSV1 virions, measuring up to 0,1 µm, in liver capillaries, near to red cells (arrows), as the infection is systemic; **C, D –** Congenital cytomegaloviruses. The H&E stained slide (C) shows renal tubular cells with the typical CMV inclusion-the owl´s eye (arrow), with cytomegaly, eosinophilic nuclear inclusion, surrounded by clear halo and granular cytoplasmic inclusions. (D) the electron microscopy shows numerous virions grouped in the nucleus (arrows), some budding from the nuclear membrane to complete its cycle in the cytoplasm (small arrow). *Magnification.* **A, C –** 400x, **B, D –** 40,000x.

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