Porcine Research

African swine fever: A brief review of the literature

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Abstract. African swine fever (ASF) is often characterized as the main contemporary disease of swine due to the high mortality in domestic pigs, severe economic consequences, and the lack of specific treatment and prevention. The rapid expansion of the virus through the European and Asian continents makes the ASF a worldly topic of veterinarians' research projects. In this review, we briefly present the current knowledge on the epidemiology, pathogenesis, and diagnosis of ASF.
Key Words: ASF, diagnostic, epidemiology, pathology.

Introduction. African swine fever (ASF) is a brutal infectious viral disease of both domestic pigs and Eurasian wild boars (*Sus scrofa*) with a very high level of mortality and lethality, approaching 100% in domestic swine (Galindo & Alonso 2017). The continuous spreading of ASF in Europe and Asia during the last period has raised the awareness of the threatening capacity of this pathology to the international pig industry and food safety associations (Dixon et al 2019). Due to the great capacity of transmission, high mortality, and the devastating impacts on the international trade of pigs and pork products, the notification of ASF to the Word Organization for Animal Health (OIE) is mandatory and essential (Gallardo et al 2019). Since there is no specific therapy, nor a licensed vaccine, the control measures rely only on strict sanitary protocols (Blome et al 2020). The aim of this manuscript was to describe the pathogenesis and the most common clinical and gross findings in ASF and to collect the most recent information regarding the epidemiology and the diagnosis.

Etiology. The ASF disease is caused by a large, complex double-stranded DNA virus of the genus *Asfivirus* from the Asfarviridae family, being the sole member of the family and genus (Dixon et al 2019). The viral genome codes around 150 and 167 proteins, many of which have a high immunogenic characteristic, and it varies between 170 and 193 kbp (Dixon et al 2013). The outer capsid of the virus forms a hexagonal lattice made from 8280 copies of the major p72 protein, and 60 copies of a penton protein at the vertices (Andrés et al 2020).

Epidemiology. The first report of the disease was in Kenya in the 1920s (Montgomery 1921), from where it spread to other African countries and Europe until the middle of the 20th century, reaching the South Americas later. With the implementation of drastic control measures and programs of eradication, the authorities successfully managed to eradicate the disease from Europe, except Sardinia, in the 1990s. The second emergence of ASF in Europe started in 2007 in the Republic of Georgia (Rowlands et al 2008), and it keeps disseminating to the west in European countries (Cwynar et al 2019) and eastwards to Asian countries, creating, in its way, severe medical, industrial and socio-economic consequences. Germany is the latest country that lost its "free of ASF" status (Sauter-Louis et al 2020). The susceptible vertebrate hosts are suids, and the only

confirmed biological vectors are the soft ticks from the *Ornithodoros* genus (Jori & Bastos 2009), making the ASF virus the only DNA arthropod-borne virus. The infection with African swine fever virus (ASFV) in wildlife African hosts does not cause evident clinical signs, except for young individuals, hence, making them, together with the soft ticks, the natural reservoir of ASFV (Jori et al 2013).

After the introduction of the virus in a domestic swine population, it can be transmitted between infected and susceptible animals by direct contact, or by indirect contact with contaminated objects, fomites, and feed (Chenais et al 2019). Traditional, rudimentary nutrition protocols including swill feeding and blood products can play an enormous role in the transmission of the virus (Wen et al 2019). The infection cycles in the wild boars' habitats are maintained by carcasses, but their role in long-term transmission is still under discussion (Ståhl et al 2019).

Pathological mechanism. ASF can be characterized by a general state of immunodeficiency, accompanied by severe leukopenia and lymphopenia (Salguero et al 2005). To understand the pathogenesis of lymphoid depletion, we need to follow the virus route through the organism. After the virus enters the body consecutively of a bite of an infected soft tick or following an oro-nasal route, the first replications take place in the regional lymph nodes or tonsils (Blome et al 2013). From this place, the virus will spread via lymph and blood circulation within 2 or 3 days to the secondary organs of replication such as liver, spleen and bone marrow. After the secondary replication has taken place, the spreading of the virus will continue to the rest of the organs, in which ASFV is capable of further replication in a variety of cells such as megakaryocytes, kidney cells (epithelial and mesangial), tonsillar epithelial cells, hepatocytes, fibroblasts and endothelial cells (Gómez-Villamandos et al 2013). The main target cells are the monocytes and macrophages (Salguero et al 2002), in which the replication takes place within the cytoplasm, not in the nucleus (Martins et al 1987). After the replication, a necrotic process of the infected cell is induced, with releasing of the virion by budding in the interstitial tissue lymph and blood (Gómez-Villamandos et al 1997). Consecutively, there will be an activation of this cell population that will induce an increased secretion of proinflammatory cytokines, such as IL-1, IL-6, and TNF-alpha, described as the "cytokine storm" (Gómez del Moral et al 1999), which is the main mechanism responsible for the high level of apoptosis induced in lymphocytes peripheral to the infected monocytes and macrophages (Salguero et al 2005).

Besides the pathogenic mechanism of lymphoid depletion, there is another syndrome that involves disturbances in the vascular system, making ASF associable with a “hemorrhagic fever” status (Salguero 2020). The main pathogenic mechanism involved in the hemorrhagic lesions encountered in the early stages of the disease is the activation of the phagocytic activity of the endothelial cells from the capillaries (accompanied by lysosome proliferation), loss of endothelial cell junctions, followed by the hypertrophy of these cells, which might end up in the total occlusion of the capillary lumen and increase of the intravascular pressure (Gómez-Villamandos et al 2013). Due to the loss of the endothelial cells following the above described "cytokine storm" initiated mainly by the infected monocytes and macrophages, the basal membrane of the capillaries will be exposed, which will allow the platelets adherence, activation of the coagulation system and finally induce widespread disseminated intravascular coagulation (DIC) (Villeda et al 1993). The intense, transient, thrombocytopenia can also play a major role in the mechanism of hemorrhages in the middle and late stages of ASF, and it is accompanied by structural changes of the megakaryocytes, with their frequent denudations in bone marrow (Bautista et al 1998).

Clinical signs. The clinical signs in ASF depend on the viral strains' virulence and individual factors such as age and immunologic status, which make the clinical aspects highly variable. The contemporary outbursts of ASF in Europe and Asia are produced by the genotype II strain, which has a high virulence for both domestic and European wild boars (Pikalo et al 2019).

The peracute form of ASF is characterized by a fulminant clinical evolution, with severe hyperthermia, up to 42°C, consecutively respiratory distress, lethargy, and anorexia, but sometimes animals can die suddenly without manifestation of any clinical signs. This evolutive form is mainly encountered when the virus reaches a naïve farm (Salguero 2020).

In the acute clinical form, mortality rates can reach up to 100% within 7 days from the debut of the clinical signs. It is characterized by high fever, usually between 40 and 42°C, anorexia, lethargy, inactivity, and the affected pigs tend to bulk up together. Cyanotic discoloration can be noticed at the level of the ears, snout, abdomen, tail, limbs, and perianal area. Usually, the affected pigs manifest respiratory distress (Carrasco et al 2002) and skin lesions such as petechial hemorrhages or ecchymosis. Infected pregnant sows may abort. Other frequent clinical signs exhibited by infected pigs are vomiting, diarrhea, or sometimes melena and soiling of the perianal area and nasal discharges accompanied by epistaxis (Sánchez-Vizcaíno et al 2015).

The mortality rate, in the subacute form of ASF, ranges between 30 to 70% (Sánchez-Vizcaíno et al 2015), and the infected pigs can die in 7-20 days after inoculation. The clinical characteristics are similar, but less marked than those observed in the acute form of ASF. The animals can die during an initial state of leukopenia and thrombocytopenia (Villeda et al 1993) or during a phase that resembles a recovery status in piglets that involves erythrodiapedesis induced by vasodilatation (Gómez-Villamandos et al 2013).

The infrequently encountered chronic clinical form of ASF has been observed only in the Dominican Republic and the Iberian Peninsula, at it is characterized by emaciation, growth retardation, respiratory distress abortion, and arthritis (Salguero 2020).

Pathological findings. The peracute clinical form does not exhibit, usually, any gross lesions.

The acute evolutive form is characterized by acute hemorrhagic splenomegaly (Figure 1A) (Konno et al 1972). Another important gross finding is the multifocal hemorrhagic lymphadenitis (Figure 1B), where lymph nodes can resemble the aspect of a blood clot or present a marble appearance. The highly affected lymph nodes are gastro-hepatic, mesenteric, ileocecal, and renal. The lung can show severe pulmonary edema (Figure 1F). The kidneys present widespread petechial hemorrhages (Figure 1C), especially in the cortical area. These hemorrhagic, mainly petechial lesions, can be encountered in the mucosa and serosa of the digestive tract (Figure 1B), urinary bladder, epicardium and endocardium (Figure 1D) (Salguero 2020).

In the peracute clinical form, all vascular changes, such as edema and hemorrhages from the acute form are present, but more intense. The most characteristic lesion of this form is represented by the massive edema in the wall of the gallbladder (Figure 1E). Furthermore, gross findings include hydropericardium, hydrothorax (Figure 1F), ascites, multifocal hemorrhages, and edema of the perirenal adipose tissue (Hervas et al 1996). The lungs present multiple patches of consolidation and multifocal pneumonia (Moulton et al 1975).

The chronic form of ASF does involve characteristic hemorrhagic lesions, and the gross lesions encountered sum up in necrotic dermatitis, arthritis, and pneumonia. Other lesions that can be observed, such as chronic pneumonia, necrotic tonsilitis, fibrinous polyserositis, might be associated with secondary bacterial infections (Sánchez-Vizcaíno et al 2015).

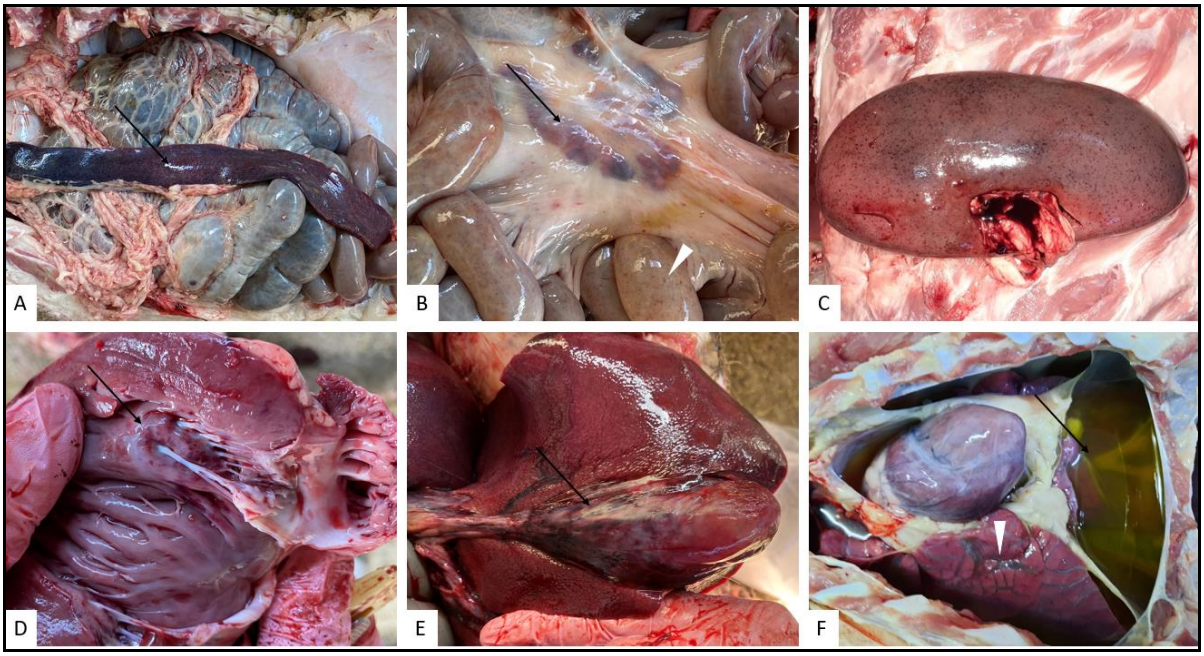

Figure 1. Gross pathological findings in African swine fever (original images): A – diffuse splenic congestion and splenomegaly; B – hemorrhagic mesenteric lymphadenitis (indicated by arrow), widespread petechial hemorrhages on the intestinal serosa (indicated by arrowhead); C – renal-cortical petechial hemorrhages; D – bubendocardial hemorrhages; E - hemorrhages and diffuse edema in the gallbladder wall; F - massive hemothorax (indicated by arrow), and hydropericardium associated with pulmonary interstitial edema (indicated by arrowhead).

Diagnostic. The confirmation of ASFV using laboratory diagnostic tests is mandatory due to the international notification requirement. All legal requirements, methods, protocols, and recommendations can be found in the Manual of Diagnostic Tests of the OIE. A large variety of ASF diagnostic techniques are approved for their confident results but, the polymerase chain reaction (PCR) is currently considered the "gold standard" method for detecting ASFV due to its superior specificity and sensitivity (Gallardo et al 2019). The rising interest regarding the global situation of ASF has created the perfect environment to improve some classic laboratory tests such as ELISA, Lateral Flow Assay (Blome et al 2020), immunohistochemistry (Salguero 2020), virus isolation, hemadsorption test (Gallardo et al 2019), colorimetric Loop-Mediated Isothermal Amplification assay (Tran et al 2020) and fluorescent immunochromatography test strips (Li et al 2020). Researching new methods of collecting samples from living pigs in order to do tests for ASFV is another trend nowadays, and an important candidate is oral fluid-based surveillance (Henao-Diaz et al 2020).

Conclusions. African swine fever remains the main disease of pigs all over the world, creating high economic loss. Since there are no specific or functional therapeutic protocols and no approved vaccines, the only way to fight with ASFV is through non-immunologic prevention. In Romania, the largest percentage of pig farms are the backyard type, in which, the implementation of the strict biosecurity protocols recommended by the OIE is almost impossible to establish. In this situation, it is especially important to raise awareness about the severity of ASF and its consequences.

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