Original Article

Histopathological Assessment of Cyclosporine and Methylprednisolone-induced Invasive Pulmonary Aspergillosis in Rabbits

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ABSTRACT

Background: *Aspergillus* is a saprophytic conidial mold usually found in different environments, like soil, decomposing organic matter, and indoor settings. This genus includes several species causing aspergillosis, a spectrum of diseases with varying clinical presentations. Among these, invasive pulmonary aspergillosis is recognized as one of the most severe forms, often leading to rapid lung tissue destruction and high mortality rates, especially in immunocompromised individuals.

Objectives: This study focused on histopathological evaluation of pulmonary aspergillosis in cyclosporine-methylprednisolone-treated immunosuppressed rabbits. The macroscopic and microscopic findings will enhance our understanding of the disease's destructive effects on lung tissue and contribute to the broader body of knowledge regarding the progression and pathology of invasive pulmonary aspergillosis in immunosuppressed hosts.

Methods: New Zealand white rabbits, treated with cyclosporine A and methylprednisolone to induce a non-neutropenic immunosuppressed condition, were endotracheally infected with *Aspergillus fumigatus* ATCC13073 conidial suspension. On days seven and thirteen post-inoculation, the rabbits' lungs were collected, and the prepared hematoxylin and eosin (H&E) slides were examined under a light microscope.

Results: The infected rabbits exhibited a 100% survival rate. Macroscopic and microscopic examinations of lung tissues revealed a progression from acute to subacute and chronic inflammatory responses on days seven and thirteen post-inoculation, respectively.

Conclusion: This study yielded valuable insights that can enhance diagnostic methods for invasive pulmonary aspergillosis in non-neutropenic immunosuppressed patients. Furthermore, these findings support the use of rabbit models as a reliable and effective system for future research on new antifungal therapies, minimizing the risk of iatrogenic mortality and property loss.

Keywords: Animal modeling, Histopathology, Immunosuppression, Pulmonary aspergillosis, Rabbit

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Introduction

Aspergillus is a genus of saprophytic fungi ubiquitously present in diverse environments, including soil, decomposing organic matter, and various indoor settings, particularly those characterized by construction dust and hospital environments (Kanj et al., 2018). Due to their small size (approximately 2-3 µm), *Aspergillus* spores are frequently inhaled and can reach the alveolar spaces. However, illness predominantly occurs in immunocompromised hosts (Ullmann et al., 2022; Fernandes et al., 2022).

Aspergillus fumigatus and *A. flavus* are significant pathogens that can cause fatal infections in immunocompromised patients. *A. fumigatus* is associated with allergic bronchopulmonary aspergillosis (ABPA), chronic pulmonary aspergillosis, and the most severe form, invasive pulmonary aspergillosis (IPA), which leads to rapid lung tissue destruction and high mortality (Rodriguez-de la Noval et al., 2020; Xu et al., 2021; Kanj et al., 2018).

In immunocompetent individuals, the innate immune response and adaptive T cell activity offer substantial protection against mild *Aspergillus* infections. Toll-like receptors activate immune defenses against fungal spores and hyphae, recruiting inflammatory cells to infection sites (Rivera et al. 2006).

Pulmonary dendritic cells, adhesion molecules, and macrophages also play crucial roles in the immune response to *A. fumigatus*. Dendritic cells mature functionally upon migrating to lymph nodes and spleens, where they regulate T-helper cell responses both locally and peripherally, and differentiate between fungal forms based on cytokine production (Banfalvi, 2018). Thus, although neutrophils, alveolar macrophages, mucus, and bronchial epithelium reveal essential impress at basic lines of immune defense against pulmonary pathogens, particularly *A. fumigatus* conidia (Kerr, et al., 2016; Xu & Shinohara, 2017; Kanj et al., 2018; Bigot et al., 2020), dysfunction in fungus-specific CD4+ T cells significantly reduces protection against IPA, especially in individuals with hematologic malignancies undergoing hematopoietic stem cell transplantation (HSCT) or chemotherapy. This dysfunction, combined with the depletion of naive CD4+ T cells, weakens immune responses, making patients more vulnerable to infections (Kanj et al., 2018). The incidence of IPA has risen, particularly among individuals with conditions, such as end-stage renal disease (ESRD), diabetes, chronic obstructive pulmonary disease (COPD), and prolonged steroid use. Additionally, many IPA patients are not neutropenic, including those undergoing corticosteroid therapy, those with graft-versus-host disease, autoimmune disorders, organ transplants, or cystic fibrosis, all of which increase susceptibility to IPA (Sun et al., 2017; Walsh et al., 2020). Immunosuppressive treatments, especially cyclosporine, a potent drug used to prevent organ transplant rejection and treat autoimmune disorders, play a considerable role in raising the risk for IPA. By inhibiting T-cell activation, cyclosporine impairs the immune system's ability to combat infections, thus increasing the risk of opportunistic infections, like those caused by *Aspergillus*, which is particularly life-threatening in these patients (Petraitis et al., 2020; Gaffney et al., 2023).

Diagnosing IPA in non-neutropenic critically ill patients is challenging due to non-specific symptoms and often delayed diagnostic tests. Early diagnosis and treatment require high clinical awareness (Bassetti et al., 2014; Bassetti & Bouza, 2017). In the ICU, revised EORTC/MSG definitions categorize IPA in immunocompromised patients as proven, probable, or possible. Proven IPA demands histopathological confirmation of fungal invasion, probable IPA requires a combination of host factors, clinical signs, and positive mycological evidence, and possible IPA is identified by host factors and clinical signs but lacks mycological confirmation (Trof et al., 2007; Rishi et al., 2016).

Histopathological evaluation is essential for assessing lung tissue lesions and disease progression in IPA, particularly in immunocompromised patients (Shibuya et al., 2004; Ledoux et al., 2020).

The establishment of animal infection models is essential for understanding the pathophysiological processes of aspergillosis, as well as for evaluating fungal virulence, diagnostic tools, and the therapeutic efficacy of antifungal drugs (Desoubeaux & Cray, 2018). Animal models are crucial in this research, with rabbits being especially valuable due to their susceptibility to respiratory infections and the similarities in their immune response to that of humans (Berenguer et al., 1995; Walsh et al., 2020).

Rabbits are phylogenetically closer to primates than rodents, making them an advantageous model for studying human-like respiratory conditions. They are particularly useful in investigating anaphylactic responses, as their lungs are a target organ for such reactions (Keir & Page, 2008). Rabbits are also universally used in scientific research to procreate hyperimmune responses and produce antibodies by bacterial suspensions or organisms' toxins

injection (Kashkooli et al., 2023; Karimi et al., 2024). Unlike other species, rabbits exhibit both early- and late-phase airway responses, enabling a detailed analysis of each phase and their connection, which is crucial for understanding asthma development (Karol, 1994). Neonatal immunization is required for rabbits to develop the late-phase airway response. Immunologically, rabbits primarily produce IgE, the key antibody responsible for initiating antigen-induced late-phase reactions in their lungs. Due to their manageable size and ease of handling, rabbits are ideal for studying lung diseases, with their size also allowing nonlethal monitoring of physiological changes (Kamaruzaman et al., 2013).

The immunophenotypic and histological characteristics observed in rabbit models treated with cyclosporine A and methylprednisolone align closely with those found in patients undergoing similar immunosuppressive therapies (Walsh et al., 2020).

The use of cyclosporine-methylprednisolone-treated rabbits allows for the simulation of an immunosuppressed state similar to that seen in human patients, providing a relevant model for studying IPA.

This study focused on the histopathological evaluation of pulmonary aspergillosis in cyclosporine-methylprednisolone-treated immunosuppressed rabbits. Detailed microscopic examination of lung tissues aimed to elucidate the pathological features associated with IPA under non-neutropenic immunosuppression. The findings will enhance understanding of IPA progression and pathology, contributing to improved diagnostic criteria and treatment strategies for immunosuppressed patients with specific conditions.

Materials and Methods

Animals

Six healthy New Zealand White rabbits, weighing 1.5-2.5 kg, were housed in individual cages. The room temperature was maintained at 21±0.05 ˚C with a 12-hour light/dark cycle, and the humidity was set at 45%. The rabbits had free access to water and rabbit chow pellets.

Microorganism and conidial suspension

To prepare inoculum, *A. fumigatus* ATCC13073 from a frozen isolate was subcultured on potato dextrose agar (PDA) and incubated at 37 ˚C for 7 days to achieve sufficient conidiation.

After that, 5 mL of sterile normal saline containing 0.05% Tween 20 was poured onto the culture medium under a laminar hood. The *A. fumigatus* ATCC13073 grown on the medium was gently scraped using a sterile loop. The resulting suspension was collected using a sterile Pasteur pipette, and the desired concentration, 1×10^8 to 1.25×10^8 conidia in a volume of 250 to 350 µL, was prepared using a hemocytometer slide and serial dilution (Petraitiene et al., 2015; Petraitis et al., 2020).

Establishment of the immunosuppressed animal model without neutropenia and invasive pulmonary aspergillosis

To establish the animal model, New Zealand white rabbits received cyclosporine (CsA) at a dose of 10 mg/kg/day (slow infusion), and methylprednisolone at a dose of 5 mg/kg/day intravenously for 14 days to induce immunosuppression without causing neutropenia. On the fourth day of the experiment, fungal inoculum was administered endotracheally to the rabbits under general anesthesia by administrating ketamine and xylazine (Berenguer et al., 1994; Petraitiene, et al., 2015). On days seven and thirteen post-inoculation, animals were sacrificed under deep anesthesia with intravenous injection of pentobarbital sodium (60-100 mg/kg), and necropsied for sampling and histopathological examination of rabbits' lungs (Figures 1 and 2).

Histopathological assessment

The collected lung specimens were fixed using 10% neutral buffered formalin for 24-48 hours for histopathological study. Next, tissue preparation was accomplished using an automatic tissue processor device (DS 2082/H; Did Sabz Co), and paraffin-embedded tissue blocks were made using a paraffin dispenser device (DS 4 LM; Did Sabz Co). The tissue sections, with a thickness of 4-6 µm (Rotary Microtome, DS 8402; Did Sabz Co), were then stained with the routine Harris Hematoxylin-Eosin (H&E) stain. The stained sections were subsequently examined under a light microscope (Motic, BA310 Epi-LED FL), and micrographs were taken using a camera (Tucsen, MIchrome 20).

Result

All infected rabbits survived throughout the study. Macroscopic and microscopic evaluations of the lungs of non-neutropenic immunosuppressed rabbits infected with *A. fumigatus* ATCC13073 revealed significant changes in lung structure due to fungal infection and inflammatory response.

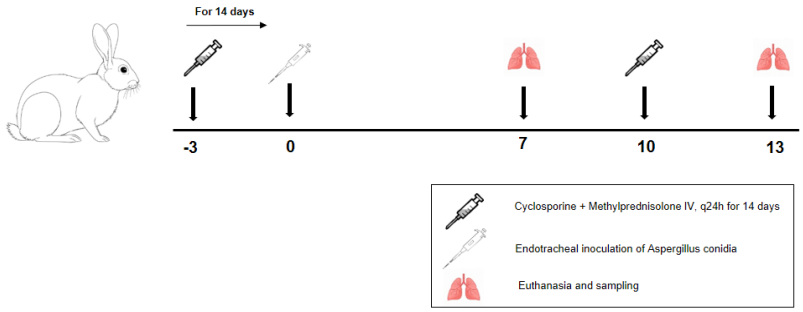

Figure 1. The schematic time point demonstrating how to make a non-neutropenic immunosuppressed rabbit model of IPA

On the seventh day post-inoculation, macroscopic examination of the lung samples revealed a variety of dark red spotted lesions, along with firm, aggregated, or confluent gray-to-white nodular lesions. Additionally, there were fewer firm, flattened, confluent gray-to-red lesions scattered throughout the lungs. Microscopically, sections of the lungs stained with H&E showed necrosis, cellular debris, focal hemorrhage, edema, fibrin deposits, foamy alveolar macrophages, and heterophil (neutrophil) infiltration. The presence of these histopathological changes indicated an acute phase of inflammatory response (Figure 3).

On the thirteenth day post-inoculation, a macroscopic examination of the lung samples revealed significant pulmonary consolidation, characterized by firm, confluent, flattened gray-to-red lesions, and firm, aggregated, or confluent gray-to-white nodules. Histopathological findings indicated fungal granulomatous pneumonia. The granulomas composed of centrally located, irregularly shaped hyphae and non-germinated conidia,

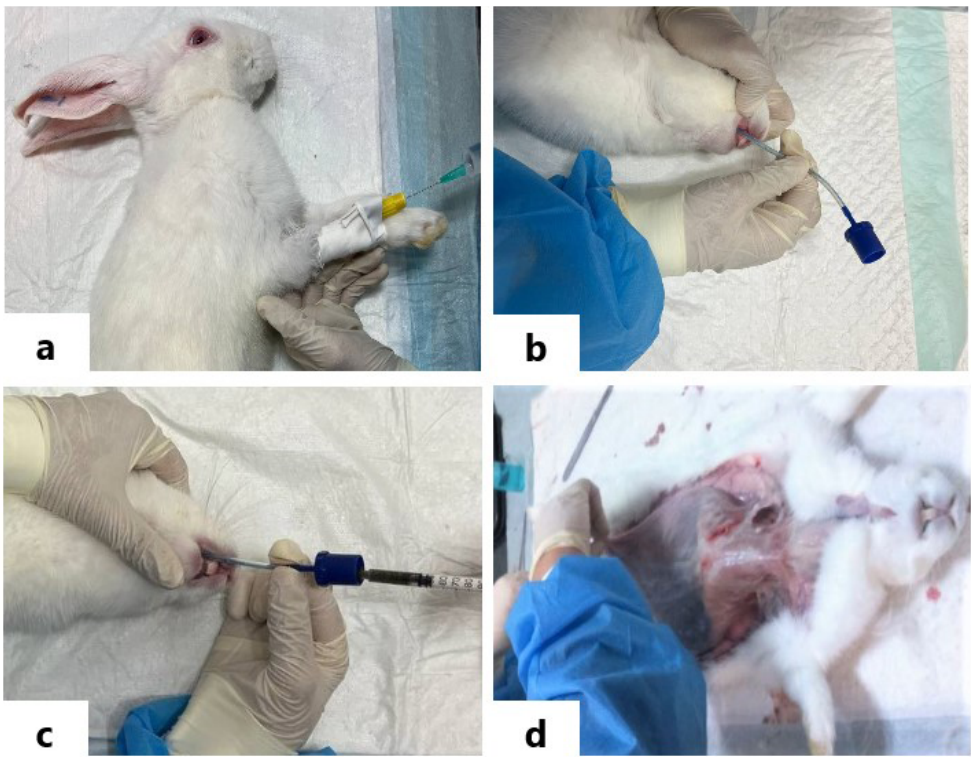

Figure 2. Figures of medication administration, anesthesia, and necropsy of a treated rabbit

a) The rabbits intravenously received cyclosporine A and methylprednisolone to obtain a non-neutropenic immunosuppressed condition, b) Under general anesthesia, an uncuffed endotracheal tube (size 2.5) was placed in the rabbit's trachea through the mouth, c) Fungal inoculum was administrated endotracheally on the fourth day of the experiment, d) Necropsy and sampling were performed on the seventh and thirteenth days after inoculation

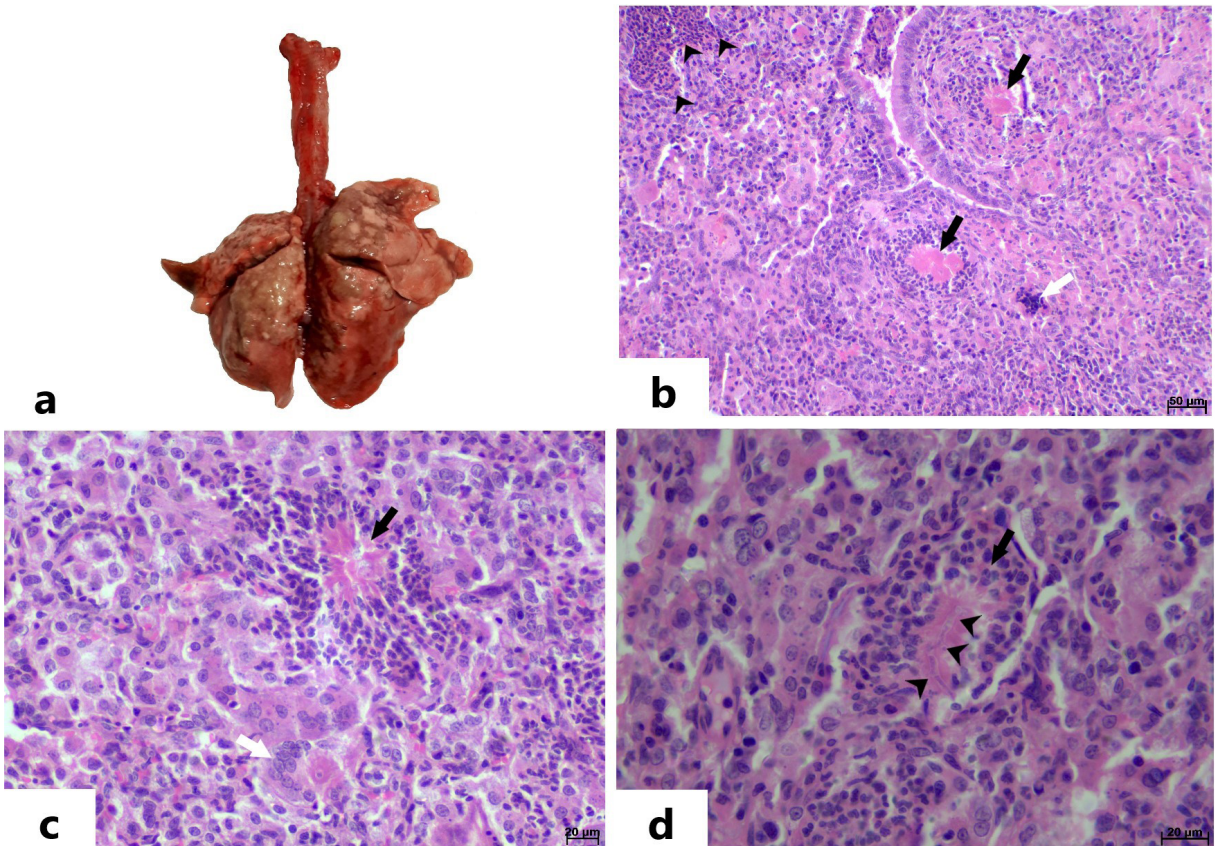

Figure 3. Rabbit lung sample on the seventh day after inoculation

a) Macroscopic view of the rabbit lung showing dark red spotted lesions indicating hemorrhage, as well as gray-white and gray-red nodules of various sizes; b) Accumulation of inflammatory cells within the bronchiole (black arrow), necrosis and cellular debris (arrowheads), and infiltration of heterophils (white arrows), H&E staining, ×20 magnification; c) Formation of Langhans giant cells (arrow) and the presence of necrosis and cellular debris (arrowheads), H&E staining, ×40 magnification; d) Formation of foreign body giant cells (black arrow), macrophages (arrowheads), and heterophils (white arrows), H&E staining, ×60 magnification

rimmed by radiating amorphous, eosinophilic, and club-like structures consisting of immunoglobulin molecules from plasmacytes. Mixed mononuclear inflammatory cells, including multinucleated Langhans and foreign body giant cells, frequently surrounded these foci, a phenomenon known as the Splendore-Hoeppli phenomenon. These findings indicated a chronic phase of the inflammatory response (Figure 4). Additional observations included type II pneumocyte hyperplasia, lymphoplasmacytic bronchiolitis, small multifocal necrosis, and cellular debris associated with heterophil infiltration.

Discussion

Among different existed studies using diverse experimental animals, including mice, rats, rabbits, and guinea pigs accompanied by various *Aspergillus* species and subspecies to establish aspergillosis animal models (Clemons & Stevens, 2005; Walsh et al., 2020), this study focused on the macroscopic and microscopic changes in the lungs of rabbits immunosuppressed with cyclosporine A and methylprednisolone and infected with *A. fumigatus* ATCC13073 at two time points: the seventh and thirteenth days after inoculation. Most previous studies have used murine models (Clemons & Stevens, 2005). Studies that have used rabbits for IPA models were often based on a persistently neutropenic immunosuppression system lasting 12-14 days (Walsh et al., 2020). Therefore, the findings of this study highlight significant differences in the pathophysiology of *Aspergillus* infection depending on the type of immunosuppression used and sampling days.

The results revealed that in the non-neutropenic cyclosporine-methylprednisolone immunosuppressed rabbit model, pulmonary lesions were classified into three major types: neutrophilic lesions, hemorrhagic infarcts, and monocytic lesions. On the seventh day post-inoculation,

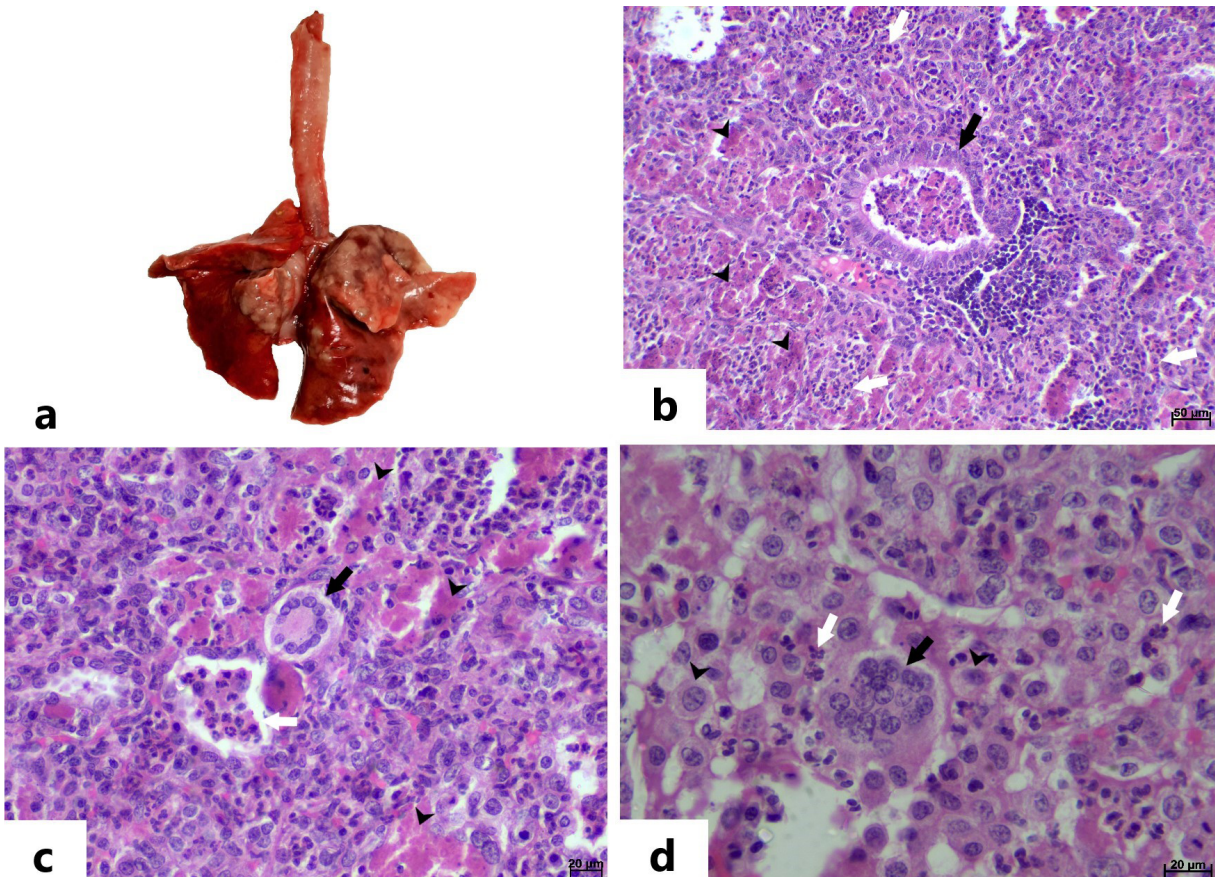

Figure 4. Rabbit lung sample on the thirteenth day after inoculation

a) Macroscopic view of the rabbit lung showing widespread involvement, with gray-white and gray-red nodules of various sizes and shapes; b) Accumulation of inflammatory cells (black arrowheads), formation of foreign body giant cells (white arrow), and the presence of the Splendore-Hoeppli phenomenon (asteroid body) (black arrows), H&E staining, ×20 magnification; c) Significant presence of macrophages along with giant cell formation (white arrow) and the Splendore-Hoeppli phenomenon (black arrow), H&E staining, ×40 magnification; d) The Splendore-Hoeppli phenomenon (arrow), composed of irregular fungal hyphae (arrowheads) surrounded by club-like structures and inflammatory cells, H&E staining, ×60 magnification

neutrophilic lesions were predominant, while hemorrhagic infarcts were focal, and monocytic lesions were less common. These pulmonary lesions showed acute to subacute inflammatory response. By the thirteenth day after inoculation, monocytic lesions became more prevalent, followed by neutrophilic and mixed lesions that composed of inflammatory responses and hyperplastic reactions. The hemorrhagic infarcts were absent. These tissue alteration indicated progression from subacute to chronic inflammatory reactions. These findings are relatively consistent with previous studies reporting some similar lesion types in rabbits using different *Aspergillus* species, such as *A. fumigatus* (Berenguer et al., 1995; Clemons & Stevens, 2005). Interestingly, this study found no mortality (100% survival) and minimal angioinvasion in the non-neutropenic immunosuppressed rabbit model. This contrasts sharply with findings in persistently neutropenic rabbits, where progressive lethal infections (100% mortality) occurred, characterized by numerous hyphal elements, angioinvasion, and extrapulmonary infection (Berenguer et al., 1995; Clemons & Stevens, 2005; Walsh et al., 2020). This stark difference emphasizes the significant impact of immunosuppressive agent selection on *Aspergillus* animal modeling to decline undesirable disadvantages and pay more attention to 3Rs in ethical use of experimental animals.

Histopathological findings in a mouse model with neutropenic immunosuppression have been limited to large abscesses of *A. fumigatus* hyphae, some inflammatory cells in the alveolar septum, and extensive lung tissue damage, including hemorrhagic infarcts, alveolar hemorrhage, fibrinous thrombi, and blood vessel destruction (Szigeti et al., 2018; Silva et al., 2018; Liu et al., 2019; Xu et al., 2021; Ali et al., 2022; Abdallah & Ali, 2022). Additionally, degeneration and desquamation of the respira-

tory epithelium, thickened alveolar walls, congestion, hemolysis of blood vessels, and infiltration of lymphocytic cell were observed (Ali & Abdallah, 2021). Compared to the current study's findings, these results emphasize the pronounced hemorrhagic lesions and tissue-destructive responses without noteworthy inflammatory reactions in neutropenic conditions. This differs markedly from the relatively controlled pathology, along with a singular variety of inflammatory cells, observed with cyclosporine-methylprednisolone immunosuppression.

In the IPA rabbit model, persistently neutropenic rabbits exhibited intraalveolar hemorrhage, coagulative necrosis, and hemorrhagic infarction due to intravascular thrombosis. Additionally, large amounts of dichotomously branching septated *Aspergillus* hyphae demonstrating angioinvasion were observed (Francis et al., 1994; Berenguer et al., 1995; Petraitiene et al., 2015; Petraitis et al., 2020). Conversely, in non-neutropenic cyclosporine-methylprednisolone immunosuppressed rabbits, extensive inflammatory necrotizing pneumonia was noted, without evident angioinvasion, extensive hemorrhage, or infarction. This presentation was characterized by scattered, irregularly shaped hyphae and non-germinated conidia (Berenguer et al., 1995; Petraitiene et al., 2015). This comparison highlights how the type of immunosuppression influences the fungal infection's presentation and severity, which is in accordance with the current study's findings.

Furthermore, a study on ostensibly healthy rabbits revealed white nodular lesions (1 to 3 mm) on the lung surface, more severe in younger rabbits. Microscopically, these nodules composed of respiratory bronchioles filled with foamy macrophages, heterophils, and cellular debris, surrounded by epithelioid cells with multinucleated giant cells that located centrally. Various- shaped hyphae surrounded by eosinophilic radiating projections and "asteroid bodies" with heterophil accumulations were also identified (Matsui et al., 1985). Our study aligns with these findings, particularly regarding the microscopic structure of nodular lesions, although we observed these features under non-neutropenic immunosuppressed conditions rather than in healthy rabbits.

In a study examining autopsied patients with invasive pulmonary aspergillosis, lesions were categorized into discrete nodules (DNs) and fused lobular consolidation (FLC). DNs were characterized by well-demarcated, round-shaped coagulative necrosis with numerous hyphae and minimal inflammatory infiltrate, typically observed in patients with severe agranulocytosis or bone marrow suppression. FLC, on the other hand, resembled bronchopneumonia and was marked by acute inflammatory exudates with proliferation of fungi within the alveoli, often leading to cavitation due to neutrophilic infiltration and necrosis (Shibuya et al., 2004). Our current findings support the FLC pattern in terms of acute inflammatory response, neutrophilic infiltration, and necrosis on the seventh day after inoculation, while extending this understanding to a rabbit model under induced immunosuppressive conditions.

Overall, our study highlights the significant influence of immunosuppressive regimens on the pathology and severity of invasive pulmonary aspergillosis. The distinct histopathological features observed in our rabbit model under cyclosporine-methylprednisolone immunosuppression provide valuable insights for developing and refining animal models with considering animal research ethics to study *Aspergillus* infections and test novel antifungal therapies. These findings underscore the importance of considering the roles of immunosuppressive agents when interpreting experimental results and their implications for human disease.

Conclusion

In summary, most studies on IPA have been conducted using mouse models, as well as the persistently neutropenic immunosuppression method commonly employed in rabbit models. Both approaches exhibit a high mortality rate, and no significant inflammatory response was observed. Most lesions were characterized by extensive fungal hyphae growth, necrosis, and hemorrhage. There are few studies using the non-neutropenic immunosuppression rabbit model, which has significant advantages, including an inflammatory response in both the acute and chronic phases, a high survival rate, and similarities to patients undergoing corticosteroid treatments or ICU admission. This model holds promise for future advanced research and for studying new antifungal compounds.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Research Ethics Committee of Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran (Code: IR.UT.VETMED.REC.1401.013).

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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