Iron and Iron Overload in Invasive Fungal Infections

Subjects: Hematology

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Iron is an essential trace metal necessary for the reproduction and survival of fungal pathogens. The latter have developed various mechanisms to acquire iron from their mammalian hosts, with whom they participate in a continuous struggle for dominance over iron. Invasive fungal infections are an important problem in the treatment of patients with hematological malignancies, and they are associated with significant morbidity and mortality. The diagnosis of invasive clinical infections in these patients is complex, and the treatment, which must occur as early as possible, is difficult. There are several studies that have shown a possible link between iron overload and an increased susceptibility to infections. This link is also relevant for patients with hematological malignancies and for those treated with allogeneic hematopoietic stem cell transplantation. The role of iron and its metabolism in the virulence and pathogenesis of various invasive fungal infections is intriguing, and so far, there is some evidence linking invasive fungal infections to iron or iron overload. Clarifying the possible association of iron and iron overload with susceptibility to invasive fungal infections could be important for a better prevention and treatment of these infections in patients with hematological malignancies.

Keywords: iron ; iron overload ; fungal infection ; hematological malignancies ; iron chelation therapy

1. Invasive Fungal Infections in Hematology

Despite some effective prophylaxis modalities, invasive fungal infections (IFI) caused by Aspergillus and Candida species, and more rarely by Zygomicetes, Fusarium or Trichosporon species, are still a common cause of morbidity and mortality in immunocompromised patients with hematological malignancies, including those who are allogeneic hematopoietic stem cell transplant recipients [1][2]. The main cause of a predisposition for IFI is the impairment of immunity that results from the pathogenesis of the malignant hematological disease itself, but also from various therapies that weaken immunity at different levels. Crucial to IFI susceptibility is an impaired innate immunity (a reduced number and function of neutrophils and macrophages), and also an impaired T cell immunity. This is why the incidence of IFI is highest in patients with acute leukemia treated with intensive chemotherapy or those who have undergone allogeneic bone marrow transplantation. The main risk factor for the development of IFI in hematological patients is a severe and prolonged neutropenia after intensive chemotherapy [3]. In hematopoietic cell transplant recipients, there are three main factors that increase the risk of IFI: mucosal damage and neutropenia as an early consequence of transplantation, severe damage and gradual recovery of T-cell immunity, and prolonged corticosteroid treatment in patients who develop acute graft-versus-host disease [4][5][6]. There are several papers that investigated the role of IFI in the hematological patients unfit for chemoimmunotherapy but treated with other emerging therapies. Aldoss et al. concluded that the overall risk of IFI during venetoclax and hypomethylating agent therapy is relatively low (12.6% patients developed probable or proven IFI in this investigation). The risk of IFI was higher in nonresponders, relapsed and refractory patients [7]. There are real-world data suggesting a slightly higher risk of IFI in patients with chronic lymphocytic leukemia treated with ibrutinib (BTK inhibitor), especially in the first six months of treatment [8][9][10].

The same could be true for PI3K inhibitors such as idelalisib [8][10][11]. All this suggests the possible importance of antifungal prophylaxis in certain groups of patients. In principle, posaconazole remains the drug of choice when the incidence of invasive mold diseases exceeds 8%, and it is strongly recommended for patients undergoing remission-induction chemotherapy for acute myeloid leukemia and myelodysplastic syndrom, as well as for preventing IFI in recipients of an allogenic hematopoietic stem cell transplantation, especially post-engraftment in the presence of graft-versus-host disease and other risk factors for IFI [12].

The diagnosis of IFI must be fast and effective, and it is crucial to start a specific antifungal therapy as early as possible, as this is the most important prerequisite for successful treatment and prevention of mortality [13]. The diagnosis of IFI itself is established by means of a combination of different diagnostic methods: microbiological cultures, microscopy, various antibody/antigen tests, molecular and imaging diagnostics. The basis of prophylaxis and forehand treatment of IFI are different antifungal drugs (triazoles, echinocandins and polyenes), as well as surgical treatment in some cases.

2. Iron and Iron Overload: Their Role in Infections

Iron, a micronutrient essential for life, participates in many vital biological processes. Ferritin is a protein that serves to store iron in the body in a non-toxic form. It is mainly located intracellularly, although a small proportion of this protein is found in the serum and correlates with the body's total iron stores [14]. When the concentration of ferritin in the body (serum) is higher than normal, researchers talk about iron overload. The latter can result from various pathological conditions, such as primary hemochromatosis or frequent blood transfusions, which are common in some hematological diseases. Elevated serum ferritin levels also occur with infections or liver damage [15]. Like humans, microorganisms also need iron for their growth and survival. Thus, fungal pathogens have developed various mechanisms to obtain iron from hosts for their own needs, which will be discussed in more detail in the following section. Hosts, including humans, on the other hand, have developed mechanisms to make iron as inaccessible to microorganisms as possible, especially during infection and concomitant inflammation (increased production of hepcidin and natural iron chelators being some of them), which probably reduces the virulence and pathogenicity of bacterial and fungal pathogens [16]. Therefore, there is a constant competitive relationship between hosts and microorganisms, including fungal pathogens, with respect to iron.

While it is well known that iron overload damages organs such as the liver, the heart, and the endocrine glands, the impact of this disorder on the immune system is less well understood (**Figure 1**). Although the diagnosis of iron overload can be confirmed by various invasive and non-invasive (imaging) methods, the simplest, most widely used, but not the most accurate method is to determine serum ferritin values; a serum ferritin value of 1000 µg/L or more is mainly used in hematology as a cut off value, which indicates treatment with iron chelators [17][18]. In their meta-analysis, Oliva and colleagues suggested that a higher concentration of serum ferritin is a prognostic indicator of shorter survival in patients with myelodysplastic syndrome, as shown by some earlier research [19][20]. Although some data suggest that non-transferrin-bound iron and labile plasma iron could have a proleukemic effect achieved through reactive oxygen species (ROS) [21][22], the two papers included in this meta-analysis did not establish a possible relationship between serum ferritin level and progression to AML [23][24]. There is evidence that iron overload stimulates the growth and survival of some microorganisms. For example, Vibrio vulnificus and Yersinia enterocolitica, the so-called "siderophylic bacteria", have been shown to cause dangerous infections, particularly in patients with iron overload [25][26][27]. Furthermore, macrophage iron overload due to chronic hemolysis in malaria has been proven to increase the risk of Salmonella infections [28]. Finally, several authors have shown that iron supplementation leads to increased morbidity and mortality from different endemic infections [29][30]. The results of a number of studies found that elevated serum ferritin or hepcidin-25 was associated with more frequent infections in hemodialysis patients and in those who underwent kidney or liver transplantation [31][32][33]. In hematology, several studies linked iron overload with a higher incidence of infections. Pre-transplantation ferritin values have been shown to be positively correlated with the incidence of bloodstream infections within 100 days of allogeneic bone marrow transplantation [34], as well as early bacterial infections after transplantation [35]. In studies of multiple myeloma, Miceli and colleagues found that iron overload is a significant risk factor for infections after autologous transplantation in patients with this type of cancer [36]. Researchers' group also found that elevated serum ferritin is an important risk factor in patients with multiple myeloma who did not undergo transplantation [37].

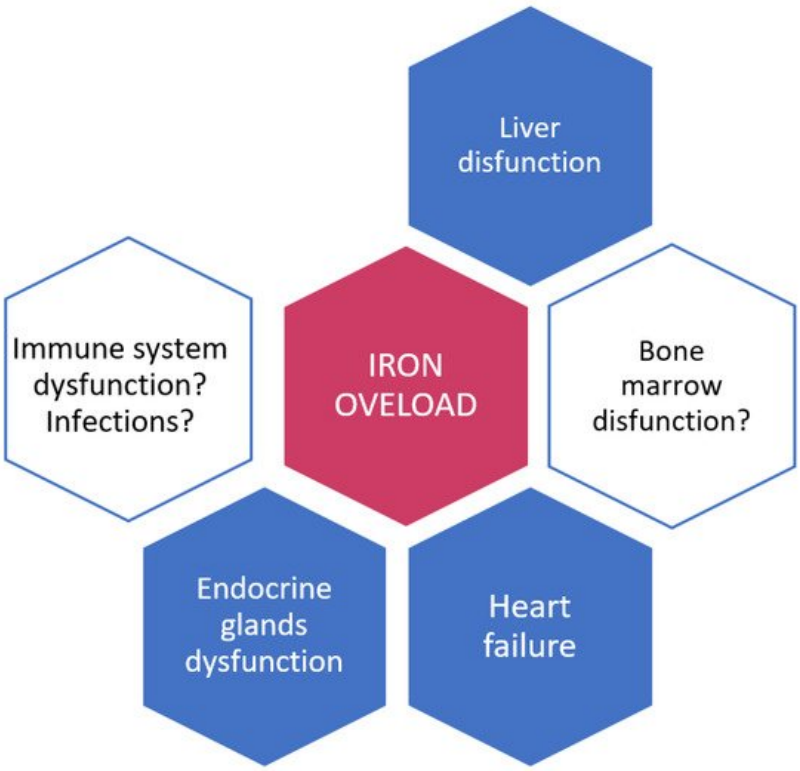

Figure 1. Effects of iron overload on target organs.

In affected organs, excess iron can chemically interact with hydrogen peroxide, creating reactive oxygen species that can cause tissue damage, inflammation, and fibrosis. As such, iron overload can lead to cardiomyopathy, arrhythmias and heart failure, liver fibrosis and cirrhosis, diabetes mellitus, hypothyroidism, hypogonadism, and impotence. The impact of iron overload on the immune system and infections is less well understood, although there are indications that iron overload stimulates the growth and survival of some microorganisms and that excessive amounts of iron in bone marrow stores act as an independent prognostic factor for invasive aspergillosis in allogenic transplant patients.

3. Mechanisms of Iron Acquisition by Fungal Pathogens

3.1. Reduction of Ferric to Ferrous Iron with Subsequent Transport

Yeast *S. cerevisiae* was used to investigate the basic mechanisms involved in the acquisition of iron by fungal pathogens. The reduction of ferric to ferrous iron with subsequent transport takes place in two stages: in order to enter the cell, the insoluble ferric iron must first be reduced to a relatively soluble ferrous iron, which is mediated by ferric reductases encoded by FRE genes (FRE1 and FRE2). The second stage consists of the re-oxidation of ferrous iron to the ferric form, which is accomplished by multicopper ferroxidase (Fet3) coupled with transport into the cell by a permease (Ftr1) [38]. This process is necessary because the ferrous form is toxic to the cell as it leads to the formation of reactive oxygen species.

C. albicans, *A. fumigatus* and *C. neoformans* use the same cell-surface-mediated ferric reductases, ferroxidases and iron permeases as described in *S. cerevisiae* [39][40][41][42][43]. Genes for other proteins that play a role in ferric reductases have been found in the genome of *C. albicans* and *A. fumigatus*, although probably not all of them are active [41][42][44][45].

3.2. Siderophore Production and Transport

Most fungal pathogens can produce and secrete siderophores, which are tiny organic formations whose most notable function is to be high affinity ferric chelators that acquire and transport iron from the microenvironment into the interior of the cell [46][47][48][49]. The *Aspergillus* species have the capacity to synthesize several types of siderophores, including ferricrocin, hydroxyferricrocin, fusarinine C, coprogen B and triacetylfusarinine C [50][51][52]. There are plenty of studies which looked at the genetics and production of siderophores, as well as their possible role in the virulence of *A. fumigatus* [53][54][55]. Despite the fact that a reductive transport system can perform a siderophore-related input, this system is most efficient in an abundance of siderophores. At lower concentrations of siderophores, entry into the cell occurs primarily through specific transporters of the ARN/SIT subfamily of the major facilitator superfamily, which are secondary transporters with 14 predicted transmembrane domains, and they likely function as proton symporters energized by the membrane potential [56][57][58].

S. cerevisiae, *C. neoformans* and *C. albicans* cannot produce their own siderophores. Instead, they use exogenous siderophores (xenosiderophores) synthesized by other microorganisms. The research on *S. cerevisiae* provided basic findings and a model for the uptake mechanisms for xenosiderophores via different transporters [56]. These transporters, such as Arn1, Arn2/Taf1, Arn3/Sit1, and Arn4/Enb1, are specific for different bacterial and fungal xenosiderophores, such as enterobactin, ferrichrome, ferrichrome A, triacetylfusarine C, and ferrioxmaine B [59]. As an example, *C. albicans* uses the Sit1/Arn1 transporter to uptake xenosiderophores such as ferricrocin, ferrichrysin, ferrirubin, coprogen and triacetylfusarine C [60].

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