

Iron metabolism and fungal infections in patients with haematological malignancies

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Abstract

Aim—To determine whether iron metabolism influences the incidence of systemic fungal infection in patients with haematological malignancies.

Methods—The study population comprised 74 patients who had undergone myeloablative chemotherapy. Systemic fungal infections were classified as confirmed (histological confirmation or characteristic septate hyphae) or possible (antibiotic resistant fever which resolved following administration of intravenous amphotericin B, together with either typical radiographic lesions or massive oropharyngeal candidiasis). Parameters of iron metabolism included serum iron concentrations, total iron binding capacity, serum transferrin, and ferritin concentrations and transferrin saturation values.

Results—Patients who developed a fungal infection had substantially increased transferrin saturation values and ferritin concentrations at diagnosis together with low serum transferrin and high serum iron concentrations. This profile was present in patients with a fungal infection regardless of the underlying haematological disorder.

Conclusion—Increased transferrin saturation values and high ferritin concentrations may be additional risk factors for the development of systemic fungal infection in patients with haematological malignancies.

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Iron metabolism in patients with chronic lymphoid or myeloid leukaemia, as in those with Hodgkin's and non-Hodgkin's lymphomas, is similar to that of chronic disorders and is characterised by the presence of low serum iron concentrations despite adequate iron stores, together with normal transferrin saturation values and slight increases in serum ferritin concentrations.¹⁻⁴ Patients with acute myeloid leukaemia (AML) are an exception as they usually have high serum iron and very high serum ferritin concentrations, and raised transferrin saturation values.⁵⁻⁸

In vitro studies have shown that iron supplementation to increase transferrin saturation

values inhibits serum fungistasis^{9 10} and some authors have suggested that there is an association between reduced total iron binding capacity (TIBC) and fungal infection in patients with acute non-lymphoblastic leukaemia.^{11 12}

The aim of this study was to determine whether iron metabolism differs in various types of haematological malignancies and whether such differences are associated with a higher incidence of fungal infection.

Methods

The clinical records of 74 patients with haematological malignancies attending the Haematology Service of the University Hospital of Salamanca were reviewed retrospectively. The only criterion for patient selection was that they should have received myeloablative chemotherapy. Apart from this, selection was blind. Of the patients, 22 had been diagnosed as having acute AML, eight as having acute lymphoblastic leukaemia (ALL), and the remaining 44 as having a chronic lymphoproliferative disorder (nine had Hodgkin's lymphoma, 26 non-Hodgkin's lymphoma, and nine multiple myeloma). It should be emphasised that this latter group also received myeloablative therapy and 10 of the 44 underwent autologous transplantation.

Systemic fungal infections were classified as confirmed or possible. For the diagnosis of a fungal infection, histological confirmation following culture of *Aspergillus spp* or the presence of characteristic septate hyphae in a relevant tissue biopsy specimen was required. A clinical diagnosis of a possible systemic fungal infection was established when the patient had antibiotic resistant fever which resolved following administration of intravenous amphotericin B and the presence of at least one of the following criteria: new pulmonary nodules or new infiltrates on computed tomography scan showing the "halo" or the "air crescent" signs, or round lesions (>1 cm in diameter) with clearly associated vascular structures; or massive oropharyngeal candidiasis. All of the patients had a positive culture in sputum or a serological profile compatible with *Aspergillus* or *Candida* infection.

In all cases the following parameters of iron metabolism were determined at diagnosis: serum iron, transferrin, and ferritin concentrations, TIBC, and transferrin saturation values. These parameters were measured using a BM/Hitachi 717 autoanalyser. Serum iron concentrations were determined using

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colorimetry; serum transferrin and serum ferritin concentrations were determined using immunoprecipitation techniques (Boehringer Mannheim, Mannheim, Germany). The TIBC and transferrin saturation values were calculated with respect to the serum iron and serum transferrin concentrations.

The Student's *t* test was used to establish the statistical significance of differences between mean values.

Results

Serum iron, transferrin, and ferritin concentrations, and the TIBC and transferrin saturation values at diagnosis in the three groups of patients studied are presented in table 1. Patients with AML and ALL had raised serum iron concentrations ($p = 0.03$), transferrin saturation values ($p = 0.02$), and serum ferritin concentrations ($p = 0.001$) compared with those with chronic lymphoproliferative disorders.

During the course of the disease, 49 of the 78 patients displayed severe infection, usually associated with granulocytopenia following chemotherapy. Of these cases, 24 had sepsis caused by Gram negative or Gram positive pathogens; in the other 25 cases a systemic fungal infection was suspected. This was confirmed histologically in four cases and diagnosed clinically in the remaining 21. The distribution of fungal infections with respect to disease diagnosis was as follows: 11 (50%) patients with AML, 11 (25%) with a lymphoproliferative disorder, and three (37%) with ALL.

On comparing iron metabolism in patients with and without fungal infection (25 and 53 cases, respectively) (table 2), the former group had significantly increased serum iron concentrations ($p = 0.01$), a lower TIBC, and serum transferrin concentration ($p = 0.001$), while transferrin saturation values and serum ferritin concentrations were significantly increased ($p = 0.001$). Iron concentrations in patients with confirmed infection on biopsy were even higher than in those diagnosed clin-

ically as having a possible fungal infection. Nevertheless, only four cases were included in the former patient group. We also sought to determine whether iron metabolism was associated with fungal infection. The patients with AML who developed a fungal infection had significantly higher transferrin saturation values (71 ± 19 v 47 ± 21 ; $p = 0.01$) and serum ferritin concentrations (1517 ± 1415 v 851 ± 773 ; $p = 0.008$) than those who did not. Patients with ALL had a similar pattern to those with AML, although the number of cases included in the study precluded meaningful statistical analysis. In patients with lymphoproliferative disorders a higher ferritin concentration was also observed in those with a fungal infection (792 ± 650 v 362 ± 320 ; $p = 0.008$), together with increased transferrin saturation values (not significant).

Discussion

The present study confirms previous results showing that patients with AML have substantially increased transferrin saturation values and serum ferritin concentrations.^{6,7,11,12} Moreover, our data indicate that this pattern is also characteristic of patients with ALL. In patients with lymphoma one would expect, as in other solid tumours,^{2,4} a pattern similar to that observed in chronic disorders. However, we observed normal serum iron concentrations and transferrin saturation values, with slightly raised serum ferritin concentrations.

A possible explanation for the increase in ferritin concentrations detected in both AML and ALL is that the blast cells could be actively synthesising ferritin and releasing it into the serum.^{13,14} Increased transferrin saturation values could result from a decrease in transferrin concentrations without a parallel decrease in the serum iron concentration. The decrease in transferrin concentrations can be explained as an acute phase reactant protein response, characteristic of chronic disorders. In contrast to other tumours, serum iron concentrations were slightly raised in patients with acute leukaemia, which may be at least partially attributed to a decrease in iron consumption caused by diminished bone marrow cell erythropoietic activity.⁵ An additional and probably a more important factor is the transfer of iron from ferritin to transferrin in the circulation.¹⁵

Iron is an essential nutrient for opportunistic fungi. They may even use iron from iron binding proteins to generate siderophores,^{16,17} or use external siderophores produced by other micro-organisms, such as desferrioxamina which is generated by *Streptomyces pilosus*.^{18,19} As far as iron metabolism in pathogenic fungi is concerned, transferrin not only plays an indirect role in iron transport, but could also have a direct effect by binding directly to filamentous fungi.²⁰

To investigate whether iron metabolism affects the incidence of systemic fungal infection, we compared iron metabolism in patients with and without fungal infection overall and in each of three groups of haema-

Table 1 Iron parameters in 74 patients with malignant haematological disorders

Parameter	AML (n = 22)	Chronic lymphoproliferative disorders (n = 44)	ALL (n = 8)
Serum iron ($\mu\text{g/dl}$)	120 \pm 54	91 \pm 49	163 \pm 136
Iron binding capacity ($\mu\text{g/dl}$)	215 \pm 63	279 \pm 74	241 \pm 87
Serum transferrin (mg/dl)	162 \pm 46	223 \pm 56	203 \pm 58
Transferrin saturation (%)	59 \pm 23	35 \pm 22	60 \pm 33
Ferritin concentration (ng/ml)	1218 \pm 1191	467 \pm 435	1336 \pm 2161

Table 2 Iron metabolism in patients with and without a fungal infection

Parameter	Without fungal infection (n = 49)	With fungal infection		
		Overall (n = 25)	Confirmed (n = 4)	Possible (n = 21)
Serum iron ($\mu\text{g/dl}$)	93 \pm 55	134 \pm 82	233 \pm 151	115 \pm 48
Iron binding capacity ($\mu\text{g/dl}$)	282 \pm 69	212 \pm 75	232 \pm 48	209 \pm 79
Serum transferrin (mg/dl)	228 \pm 50	179 \pm 51	180 \pm 44	179 \pm 52
Transferrin saturation (%)	37 \pm 24	58 \pm 26	76 \pm 24	54 \pm 25
Ferritin concentration (ng/ml)	442 \pm 474	1279 \pm 1329	1898 \pm 1889	1148 \pm 1208

tological disorders. On diagnosis, patients with fungal infection had substantially increased transferrin saturation values and ferritin concentrations, together with low serum transferrin and high serum iron concentrations. This pattern was observed in patients with AML and ALL as well as in those with chronic lymphoproliferative disorders. In the latter group, however, the increase in transferrin saturation values and ferritin concentrations was not as noticeable.

Our observations confirm those of Karp and Mertz¹² who reported an association between reduced TIBC and fungal infection in patients with acute myeloblastic leukaemia. Our findings also show that the risk of sustaining mycoses with increased transferrin saturation values is not exclusive to AML, but can be extended to all malignant haematological disorders and that the fungal infection may be either candidiasis or aspergillosis. This is consistent with *in vitro* studies which demonstrated that increases in transferrin saturation values^{9,10} and decreases in serum transferrin concentrations²⁰ abolish fungistatic activity in serum.

Factors promoting the development of systemic fungal infection in patients with haematological malignancies include neutropenia, compromised immunity, and treatment with broad spectrum antibiotics. The increase in transferrin saturation values is probably an additional risk factor which, when associated with those listed previously, predisposes the patient to systemic fungal infection. Increases in transferrin saturation values probably promote fungal growth by increasing the supply of iron. One possible host defensive mechanism would be to block this supply by keeping iron either bound to apotransferrin and apolactoferrin in the extracellular space or as intracellular ferritin and hemosiderin.²¹ Saturation of extracellular proteins facilitates the release of iron and favours its presence in the free state in serum.²² Another less likely possibility is that unsaturated transferrin could have fungistatic activity²⁰ and that saturation with iron could abolish such activity.^{9,10}

In conclusion, our results suggest that there may be a correlation between fungal infection

and iron metabolism and that apotransferrin may be of use in the prophylaxis and treatment of such infections.

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