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Chronic disseminated candidiasis in patients with hematologic malignancies. Clinical features and outcome of 29 episodes

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Background and Objectives. To evaluate the characteristics of patients affected by hematologic malignancies who developed a chronic disseminated candidiasis (CDC), and to ascertain the factors that influenced the outcome, in a retrospective study conducted between January 1990 and December 2000, in 4 Hematology Divisions.

Design and Methods. CDC was diagnosed by clinical features combined with radiological and/or histologic and/or microbiological data.

Results. Twenty-eight patients (male/female 14/14; average age 42 years, range 12-67) developed a CDC. Twenty had acute myeloid leukemia, 5 had acute lymphocytic leukemia and 3 had non-Hodgkin's lymphoma. All patients received chemotherapy, including cytarabine for 21 of them (75%). Before the infection, 22 patients (79%) were neutropenic (absolute neutrophil count $<0.5\times10^9$/L) for an average of 20 days (8-36), but at CDC diagnosis only 3 patients (11%) were neutropenic. Twenty-two patients (75%) received antifungal prophylaxis for an average of 15 days (10-60). Before diagnosis of CDC, 9 patients (32%) had a candidemia. The sites compromised by CDC were: liver in 27 patients (96%) and/or spleen in 11 patients (38%). Ten patients had other organs involved: lung in 6 patients (21%), kidney in 4 patients (14%), other sites 2 patients (7%). Abdominal ultrasonography was positive in 96% of patients (27/28), and abdominal computed tomography-scan was positive in 100% of cases in which it was performed (21/21). Liver biopsy was positive in 10/15 patients (67%). The main signs and symptoms were: fever 86%, abdominal pain 54%, diarrhea 32%, tenderness 25%, vomiting 25%, jaundice 29%, dysphagia 7%. Among chemical analyses, the most sensitive test was alkaline phosphatase, with a 3-5-fold increase in 24 patients (86%); an increase of liver transaminases and γ-glutamyl transferase was observed in less than 50% of patients. By 30 days after diagnosis 4 patients had died, 1 from infection, and 3 progression of the hematologic malignancy without signs of active CDC. Within 3 months from diagnosis 14 out of the remaining 24 patients (58%) received further chemotherapy: in particular, 2 patients underwent transplantation procedures.

Interpretation and Conclusions. In our experience CDC is not a fatal complication of patients with hematologic malignancy, on the contrary to that observed for other fungal infections (i.e. aspergillosis, candidemia), characterized by a higher mortality rate. The major problem of this fungal complication is correlated to the delay in the following treatment for the hematologic malignancy with a high risk of progression of malignancy.

Key word: *Candida*, abscesses, leukemia, lymphoma.

The proportion of patients affected by malignancies who develop deep fungal infections has increased dramatically during recent decades.[1-3] Most of these infections occur in patients with hematologic malignancies and particularly in those affected by acute myeloid leukemia. This increase is due to various factors: a host defense impairment due to intensive cytotoxic chemotherapies, including transplantation procedures, ablative radiation therapy, use of corticosteroids or cyclosporine, as well as the course of the underlying hematologic disease. Other causes that favor the onset of a deep fungal infection in these patients can be environmental contamination, total parenteral nutrition (TPN), barrier disruption following cytotoxic chemotherapy, prolonged use and number of broad-spectrum antibiotics administered, use of central venous catheters (CVC).

Candida spp. are the most frequent cause of invasive fungal infection in neutropenic patients,

as demonstrated in various clinical and post-mortem studies.[4,5] Most frequently the main clinical manifestation of *Candida* infection is candidemia,[6,7] however the observation of chronic disseminated candidiasis (CDC) is not rare.[8-11]

In this retrospective analysis we reviewed the clinical features of 28 patients affected by hematologic malignancies who developed a CDC in order to evaluate the clinical spectrum of the disease, the diagnostic tools, the antifungal approach, and the outcome in this kind of patient.

Design and Methods

Charts of all patients with hematologic malignancies who developed CDC and were hospitalized at 4 different Hematological Departments of General Hospitals, between January 1, 1990 and December 31, 2000, were retrospectively evaluated.

Diagnostic criteria

The diagnosis of CDC was based on fever unresponsive to broad-spectrum antibiotics while neutropenic, and persisting after recovery from neutropenia, associated with the following clinical signs and symptoms: upper abdominal pain or tenderness, jaundice, hepatomegaly and/or splenomegaly. These clinical signs were associated with an increase of serum liver function tests, and with abnormal findings on hepato-splenic imaging by computed tomography (CT) scan or ultrasound abdominal examination consistent with CDC, as previously reported,[12,13] or histopathologic evidence of *Candida spp.* in the biopsy specimens. Furthermore, there had to be an absence of clinical or laboratory evidence of other infections and/or clinical conditions that could account for the aforementioned findings.

Diagnoses of proven, probable or possible infection were made according to recent criteria established by the *European Organization for Research and Treatment of Cancer and Mycoses Study Group* (EORTC/MSG).[14]

Antifungal treatment was started on the basis of the previously reported criteria.

Response to the treatment indicated the disappearance of all signs and symptoms of infections and normalization of liver function tests, with a reduction or disappearance of all known lesions shown by CT scan or ultrasound abdominal examination and no development of any new lesion.

Candida colonization was considered when positive throat, urine, or rectal surveillance cultures were found.

Candida attributable mortality was considered when patients died with microbiological, histologic, or clinical evidence of active fungal infection.

Data collection

Hospital records of patients with CDC were reviewed to obtain data regarding demographic characteristics (age, gender), type and stage of hematologic malignancy, and type of previous treatment for malignancy. We considered all clinical and laboratory data of patients at least 30 days before the CDC diagnosis, as well as prior microbiological documentation of deep fungal infection and/or fungal or bacterial sepsis, prior steroid and antibiotic administration, antimycotic prophylaxis, presence of positive surveillance cultures (stool, sputum, skin), degree and duration of neutropenia before the microbiological diagnosis of CDC. At the beginning of CDC we evaluated the clinical presentation of infection, the neutrophil count, antifungal treatment administered, type of drugs employed, total doses and duration of treatment. Follow-up at 6 months after CDC diagnosis was evaluated.

A *post-mortem* evaluation was carried out in all patients who died during the study period.

Results

During the study period 28 episodes of CDC were observed. According to EORTC/MSG[14] criteria the diagnosis of CDC was: proven infection in 18 patients (64%), probable infection in 8 patients (29%) and possible infection in 2 patients (7%).

Fourteen of these patients were males and fifteen were females; their median age was 42 years (range 17-67).

Hematologic malignancies

The underlying hematologic diseases of patients were the following: acute myeloid leukemia (AML) in 20 patients (71%); acute lymphoblastic leukemia (ALL) in 5 patients (18%); non-Hodgkin's lymphoma (NHL) in 3 patients (11%). All patients had received previous chemotherapy, including cytarabine in 21 cases (75%). In particular 3 patients developed CDC during transplantation procedures (2 patients autologous bone marrow transplantation (aBMT) and 1 patient alloBMT).

The majority of CDC episodes (15 cases, 54%), were diagnosed in patients who had already recovered from post-chemotherapy aplasia in hematologic complete remission. In the other 13 cases (46%) CDC developed before a chemotherapy evaluation was made.

In 12 episodes (43%) patients received corticosteroids for treatment of underlying malignancy (6

AML, 5 ALL, 1 NHL).

At the beginning of fever only 2 patients (7%) had an *in situ* central venous catheter (CVC).

Before the onset of CDC, 22 patients (79%) had been neutropenic, with an absolute neutrophil count (ANC) $<0.5\times10^9$/L, for a median time of 20 days (range 8-36).

At the time of diagnosis of CDC, in contrast, 25 patients (89%) had an ANC $>1\times10^9$/L. The median value of the neutrophil count was 5.5×10^9/L (range 0.4-22.8).

Previous antifungal prophylaxis has been administered in 22 episodes (79%). Oral polyenes, oral amphotericin B (AmB) or nystatin had been used in most of the cases (19 episodes, 86%); systemic prophylaxis had been employed only in 3 episodes (14 %), in 2 cases with fluconazole, 150 mg/daily, and in 1 case itraconazole, 400 mg/daily.

Nine patients (32%) had a documented previous fungemia during the aplasia: *Candida albicans* (5), *Candida parapsilosis* (1), *Candida krusei* (1), *Candida tropicalis* plus *Candida lipolytica* (1), *Candida albicans* plus *Candida tropicalis* (1). The median latency between last positive blood culture and CDC onset was 20 days (range 13-32).

Clinical presentation and laboratory findings

The clinical and laboratory characteristics of patients with CDC are reported in Tables 1 and 2.

Twenty-four patients (86%) had fever as the primary symptom. Among the other symptoms 15 patients had abdominal pain (54%); 7 patients showed tenderness (25%); 5 patients had diarrhea (17%); 7 patients presented vomiting (25%) and, more rarely, only 2 patients (7%), dysphagia. Eight patients (29%) had jaundice, 7 patients (25%) showed splenomegaly and 15 patients (54%) showed hepatomegaly.

The bilirubin level ranged from 0.1 to 6.1 mg/dL (median value 0.8) with a value higher than normal in only 6 patients (21%).

The alkaline phosphatase was altered, with a 3-5 fold increase over normal, in 24 patients (83%) [median value 303 IU/L (range 69-1963)]. The AST and ASP values were increased in 8 (29%) and 14 (50%) patients respectively [AST- median value 85 IU/L (range 11-589); ASP-median value 47 IU/L (range 11-325)].

In 27 patients (96%) the main site of involvement of CDC was liver. It was the sole localization in 11 cases (39%), while in the other 17 patients one or more of the following sites were involved: lung (6), kidneys (4), paranasal sinus (1), and bowel (1). Splenic involvement was reported in 11 cases (39%). The only case without liver localization, presented spleen, lung and kidney lesions.

Table 1. Clinical characteristics of 28 patients with hematologic malignancies and CDC.

Median age (range)	42 (17-67)
Sex (M/F)	14/14
Hematologic malignancy	
Acute myeloid leukemia	20 (71%)
Acute lymphoid leukemia	5 (18%
Non-Hodgkin's lymphoma	3 (11%)
Sites of infection	
Liver	27 (96%)
Spleen	11 (39%)
Lung	6 (21%)
Kidneys	4 (14%)
Paranasal sinus	1 (3%)
Bowel	1 (3%)
Symptoms	
Fever	24 (86%)
Abdominal pain	16 (57%)
Tenderness	7 (25%)
Diarrhea	5 (18%)
Vomiting	7 (25%)
Dysphagia	2 (7%)
Signs	
Jaundice	8 (29%)
Hepatomegaly	15 (54%)
Splenomegaly	7 (25%)
Outcome	
Recovery	27 (96%)
Death from infection	1 (4%)

Table 2. Laboratory findings of patients at the onset of CDC.

	Patients	*%*
Neutropenia (< 500/m³)	4/28	14
Anemia (Hb < 10 g/dL)	27/28	96
Alkaline phosphatase	24/28	86
AST	8/28	29
ASP	14/28	50
Bilirubin level	4/28	14
γ-GT	12/28	43

Diagnostic procedures

The results of the diagnostic procedures are reported in Table 3.

Before diagnosis of CDC, 16 patients (57%) had multiple positive surveillance cultures (stool, sputum, skin). Fourteen of them were positive for *Candida albicans*, and 2 for *Candida krusei*.

Abdominal ultrasound study was performed in 27 patients (96%) and in all cases revealed a non-homogeneous hepatic and/or splenic parenchyma with numerous hypoechogenic areas, most of them

Table 3. Diagnostic procedures in 28 patients with CDC.

Case	Antifungal prophylaxis	Previous fungemia	Fungal colonization*	Abdominal Ultrasound	Abdominal CT-scan	Histologic findings	Microbiological findings	Outcome	Specific diagnostic category**
1	Topical	*C. albicans*	–	+	n.d.	+	C.albicans	D /L	Proven
2	Topical	*C.albicans*	–	+	n.d	n.d	n.d.	D /I	Proven
3	Topical	*C.parapsilosis*	–	+	n.d	n.d	n.d.	Alive	Proven
4	Topical	–	*C.krusei*	+	+	n.d	n.d.	D /L	Probable
5	Topical	–	*C.albicans*	+	+	n.d	n.d.	Alive	Probable
6	Topical	–	*C.krusei*	+	n.d	–	–	D /L	Probable
7	Topical	–	*C.albicans*	+	n.d	+	–	Alive	Proven
8	Topical	*C.albicans*	–	+	n.d	–	–	Alive	Proven
9	Topical	–	*C.albicans*	+	+	n.d	n.d.	Alive	Probable
10	Topical	–	*C.albicans*	+	+	n.d	n.d.	Alive	Probable
11	Topical	*C.albicans*	*C.albicans*	+	+	–	–	Alive	Proven
12	No	–	*C.albicans*	+	+	+	–	Alive	Proven
13	Topical	–	*C.albicans*	+	n.d	–	–	Alive	Probable
14	Topical	–	*C.albicans*	+	+	+	–	Alive	Proven
15	No	–	–	+	+	–	–	Alive	Possible
16	Topical	–	*C.albicans*	+	n.d	n.d	n.d.	Alive	Probable
17	Topical	*C.albicans*	–	+	+	n.d	n.d.	Alive	Proven
18	Topical	–	*C.albicans*	+	+	n.d	n.d	Alive	Proven
19	Fluconazole	*C.albicans*	*C.albicans*	+	+	n.d	n.d.	Alive	Proven
20	Itraconazole	–	–	+	+	n.d	n.d.	Alive	Possible
21	No	–	–	+	+	+	–	Alive	Proven
22	No	*C.krusei*	–	+	+	n.d	n.d.	Alive	Proven
23	No	–	*C.albicans*	+	+	n.d	n.d.	Alive	Probable
24	Fluconazole	–	–	+	+	+	*C.incospicua*	Alive	Proven
25	No	–	–	+	+	+	*C.parapsilosis*	Alive	Proven
26	No	–	–	n.d.	+	+	*C.parapsilosis*	Alive	Proven
27	Topical	–	*C.albicans*	+	+	+	*C.albicans*	Alive	Proven
28	Topical	*C.tropicalis*	*C.albicans*	+	+	+	*C.tropicalis*	Alive	Proven

*n.d.= not done; D/L= death from leukemia; D/I= death from infection; *stool, sputum, skin; **according to EORTC/MSG criteria. Topical = oral amphotericin B or nystatin.*

showing the typical *bull's eye* appearance, in the liver and/or spleen.

All the 21 patients who underwent CT scanning showed the characteristic finding of CDC: hepatomegaly and multiple, small, circular or oval areas of decreased attenuation involving the liver (all patients); similar lesions were observed in the spleen (11 patients). The CT scan showed lesions compatible with fungal abscesses also in lung, kidneys, paranasal sinus, and bowel. Magnetic resonance imaging (MRI) was never performed at diagnosis of CDC.

Histologic examination of the sites infected was performed in 15 patients (54%) with laparoscopy in 4 cases, and ultrasound guided-needle liver biopsy in 11 cases. At laparoscopy, macroscopic examination revealed multiple, circular, yellowish foci on the surface of the enlarged liver. Histologic examination of the selectively obtained liver biopsy material showed fungal mycelia in 7 cases, while in another 4 patients the biopsy material displayed necrotic zones and small granulomatously demarcated abscesses. In 5 patients the material obtained by ultrasound guided-needle liver biopsy was not diagnostic.

In 6 of the 15 patients who had biopsies, a microbiological diagnosis was also made, and showed *Candida albicans* in 2 cases, *Candida parapsilosis* in 2 cases, *Candida tropicalis* and *Candida incospicua* in 1 case each.

At the onset of the clinical and radiological picture suggestive of CDC, blood cultures for bacteria or fungi were performed in all patients but in none of them resulted positive.

Treatment and outcome

All patients were treated with antifungal agents. When CDC was recognized, amphotericin B (AmB) was the most frequent drug employed. Deoxycolate AmB was administered in 19 cases (68%), combined with 5-fluocytosine in 5 patients and with fluconazole in another 7 patients. The median cumulative dose of AmB was 1.75 g (range 0.6 to 7.45 g). Three patients were treated with liposomal AmB (total

doses: 1.2 g, 1.6 g and 1.05 g). The remaining 6 patients (21%) received intravenous fluconazole with a median dose of 33.6 g (range 4.6 to 56 g). In one patient, unresponsive to AmB, CDC was successfully treated with i.v. caspofungin.

Intravenous antifungal therapy was continued until fever disappeared and laboratory parameters (i.e. alkaline phosphatase) returned within normal range; then all patients received oral fluconazole (200-400 mg/day) for at least 3 months (range 3-8 months), except those patients (3 cases) in whom *C. krusei* had been previously detected. These patients were given oral itraconazole (400 mg/day).

An improvement of the clinical status with disappearance of clinical manifestations and radiological pattern was observed in 27 patients (96%). In 1 patient therapy was not efficacious and he died of progression of infection. Moreover, 3 patients, although symptoms correlated to the infection improved, died within 60 days from CDC diagnosis because of the progression of the hematologic disease.

Within 3 months from diagnosis, 14 out of the remaining 24 patients (58%) received further chemotherapy. In particular 2 patients underwent BMT procedures without fungal relapse. The treatment schedule for the hematologic malignancy was delayed in all patients (46%) due to the persistence of radiological lesions.

Discussion

Despite the increase in the last years of filamentous fungi infections (*Aspergillus*, Mucorales, and *Fusarium*),[15-17] it is well known that infections due to *Candida spp.* remain the most frequent infections in neutropenic patients. The most relevant clinical manifestation is candidemia, which is characterized by a high mortality rate, ranging between 18% to 30% in different series;[6,7] other clinical manifestations due to *Candida spp.* can be observed, in particular CDC.[8-11]

CDC occurs in a small subgroup of patients with hematologic malignancies. Intensive cytotoxic chemotherapy schedules administered for the treatment of the underlying malignancy and the following neutropenia are associated with the development of this complication.

The incidence of CDC in hematologic patients is highly variable according to the different series. In the majority of cases the incidence is evaluated only in patients with acute leukemia, who represent the most relevant population at risk. The lack of prospective studies and the difficulty in making the diagnosis may account for the absence of accurate estimates on the incidence of CDC, which is reported to range from 3% to 7% in this kind of patient.[18,19]

Some authors consider CDC a late manifestation of earlier candidemia suggesting that antimycotic therapy should be started in the presence of persistent unresponsive fever to broad-spectrum antibiotic treatment without any signs that could justify it (i.e. progression of hematologic diseases), before the CDC becomes demonstrable by ultrasound or CT scan.[20] Other authors suggest that CDC is secondary to the passage of fungal hyphae from a colonized gastrointestinal tract to the portal and systemic circulation, through ulcerations induced by cytotoxic treatment (including especially Ara-C).[21] This dissemination results in seeding of the liver, spleen and possibly other visceral organs. Although a large part of our patients received chemotherapy including cytarabine (22 patients), only 12/22 (54%) had stool colonization that could justify this pathogenesis.

The diagnosis of CDC is often difficult because cytologic, histologic, and microbiological findings may remain negative. The histologic examination is the most reliable diagnostic procedure. Usually it is characterized by a strong inflammatory reaction that appears around the fungal organisms after the recovery of neutrophils, and the number of fungal organisms inside the foci may be small. However, due to the bad clinical condition of the patient, the biopsy is frequently delayed and the result of histologic evaluation is not diagnostic. In our series, biopsy resulted positive in 11 of 15 cases in which the procedure was performed (73%).

Imaging methods such as CT-scanning and ultrasonography are useful for diagnosis, but these do not always succeed in distinguishing fungal abscesses in active phase from possible, even if rare, bacterial and tubercular etiologies.[22,23]

In our study the majority of patients underwent either abdominal ultrasonography or CT-scan. In the major part of them, the ultrasonography was not less sensitive than CT-scan in identifying and localizing the hepatic and/or splenic lesions. However, high resolution CT-scans can be useful to demonstrate the presence of very small lesions, not evident by ultrasonography.[12,13,24,25] The major problem of these procedures is connected to a better analysis of details in order to identify specific signs of previous infection now cured. In these cases MRI could be more helpful, with its higher sensitivity and specificity,[26] and could be the main tool for following patients' response and activity of the fungal lesions in conjunction with clinical and lab-

oratory parameters (i.e. alkaline phosphatase).[19] In our series this examination was rarely performed due to either the recent introduction of this technique in comparison with the long study period and to its more expensive cost than CT-scan and echotomography.

On the other hand, in our experience, we observed a significant relationship between the normalization of alkaline phosphatase and recovery from the fungal complication, confirmed frequently also by a disappearance, at the serially performed ultrasonography, of hepatosplenic lesions. Polymerase chain reaction (PCR), as recently suggested, could also have an important role confirming microbiological recovery when radiological procedures show a doubtful picture because of probable fibrous results.[27]

Amphotericin B could be considered the drug of choice for the treatment at diagnosis, followed by oral fluconazole for a prolonged period (at least 4-6 months). However different studies, in the last years, demonstrated a similar, or in some cases, a better efficacy of high doses of fluconazole as initial treatment.[28] However, the observation of a change of epidemiology of *Candida spp.* infections, with an increase of the non-albicans species[29,30] that often are unresponsive to fluconazole, suggests its use only in microbiologically documented infections. Other drugs, such as amphotericin B lipid formulation, have demonstrated their high efficacy,[19,31] as confirmed in our patients treated with liposomal amphotericin B.

Only one patient died of CDC, but 11 patients had to delay the treatment for their underlying malignancy for a prolonged period because of the persistence of lesions at abdominal ultrasonography or a CT scan suggestive of active infection. Seven of these patients, who had previously achieved a hematologic complete remission, relapsed within a few months and died of progression of the underlying hematologic disease.

In conclusion, CDC is a typical systemic form of fungal infection that occurs in a high percentage of leukemia patients, particularly during the prolonged periods of neutropenia following intensive chemotherapeutic regimens. The diagnosis is frequently difficults because of the possible absence of positive microbiological and histologic findings. The infectious-related mortality rate is very low, but on the other hand the major problem of this fungal complication is correlated to the delay in the following treatment of the hematologic malignancy with a high risk of progression of malignancy. New drugs, such as voriconazole or caspofungin could be very useful, particularly in reducing the duration of treatment of this complication.

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LP co-ordinated the study; LP, LM and LF wrote the paper; MET and LM were responsible fo the data analysis; all the other co-authors collected the clinical data; GL critically reviewed and approved the final version. This work was supported by a grant from the Ministry of University and Scientific and Technological Research (MURST) of Italy.

Disclosures

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Peer Review Outcomes

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Dr. Enric Carreras, who acted as an Associate Editor. The final decision to accept this paper for publication was taken jointly by Dr. Carreras and the Editors. Manuscript received January 10, 2002; accepted March 18, 2002.

What is already known on this topic

Chronic disseminated candidiasis is a very well known complication of patients with hematologic malignancies receiving chemotherapy.

What this study adds

This topic, not previously treated in Haematologica, can be reviewed by this large and very well evaluated series, one of the first in that the new and useful EORTC/MSG diagnostic criteria have been used.

Potential implications for clinical practice

As the series shows, the infection can be controlled in most cases and does not preclude further chemotherapeutic treatments.

Enric Carreras, Associate Editor