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NOCARDIA INFECTION IN RENAL TRANSPLANT RECIPIENT: DIAGNOSTIC AND THERAPEUTIC CONSIDERATIONS

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SUMMARY

In the present report the authors discuss the diagnostic difficulties, therapeutic measures and the clinical course of *Nocardia* infection which occurred among renal transplant recipients at the University Hospital of the Faculty of Medicine of Ribeirão Preto, University of São Paulo (UH-FRP), from 1968 to 1991.

Among 500 individuals submitted to renal transplant, 9 patients developed Nocardiosis at varying times after transplant (two months to over two years). All the patients had pulmonary involvement and their most common symptoms were fever, cough and pleural pain.

Dissemination of the process is common and three patients presented cutaneous abscesses, four CNS involvement and one had pericarditis due to *Nocardia*.

The diagnostic is quite difficult since there is no specific clinical picture, concomitant infections are frequent and the microorganism presents slow growth in culture (ranging from four to forty days, in our experience). In this report, three cases were only diagnosed by necropsy.

The treatment of choice is a combination of Sulfamethoxazole and Trimethoprim (SMX-TMP).

In the present series, overall mortality was 77% (7 cases) and in five of the patients who died the diagnosis was late. All the patients who had CNS involvement died.

KEY WORDS: Renal transplant; *Nocardia* infection

INTRODUCTION

Renal transplantation is a valuable therapeutic procedure for patients with end-stage renal disease. Within this context, the success of the transplant is directly related to the use of immunosuppressive drugs which, although providing control of graft rejection, can also favor the occurrence of infectious complications with a frequently fatal outcome.

In a study conducted in Brazil, REIS [19] demonstrated that most of the deaths occurring among renal transplant recipients were caused by infections which often were not diagnosed during patient's life time.

With the objective of providing elements for earlier diagnosis and treatment, in the present report we discuss the diagnostic difficulties, therapeutic measures and the clinical course of *Nocardia* infection which occurred among renal transplant recipients at the University Hospital of the Faculty of Medicine of Ribeirão Preto- University of São Paulo (UH-FMRP), from 1968 to 1991.

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MATERIAL AND METHODS

The medical records of 500 individuals submitted to renal transplant at UH-FMRP from 1968 to 1991 were analyzed retrospectively. In 9 patients in whom it was possible to establish a diagnosis of *Nocardia* infection, the following parameters were investigated: sex, age, profession, immunosuppressive drugs in use, time of onset of *Nocardia* infection in relation to the transplant, clinical presentation, organs or systems involved, methods employed to confirm diagnosis, treatment used, and clinical outcome.

The microorganism was identified on the basis of its morphological and staining characteristics in histological sections and/or on the basis of isolation in culture. Species identification was made possible by biochemical tests [15] (Table 3). In three patients (patients 5,7 and 9), the diagnosis was established during necropsy: histological sections with the presence of filamentous, ramifyed bacteria, stained by Gram and Methenamine Silver [22].

RESULTS AND DISCUSSION

Patient's data are listed in Table 1. Age ranged from 19 to 36 years (median, 33 years) and seven patients were males. The reasons for the predominance of males, which has been commonly reported in literature [11, 16, 23], are still unknown [2].

Nocardia infection in renal transplant recipients has been reported to start one month after the beginning of immunosuppression [3, 11, 18]. However, six of our patients developed the infection during the first 6 months after surgery; the remaining three patients two years after transplantation, one of them after the use of high corticosteroid doses to control a rejection episode. For immunosuppressive therapy, seven patients were in use of azathioprine and prednisone, another one was using cyclosporine and prednisone, and the other azathioprine, cyclosporine and prednisone.

There is no suggestive clinical picture of *Nocardia* infection. However, since the lungs are frequently involved since the onset of infection, pulmonary manifestations are frequent [4, 7, 10, 16, 23]. All of the patients had pulmonary involvement (Table 2) and their most common symptoms were fever, cough and pleural pain. The radiologic features observed included nodular infiltrates (55%) and abscesses (22%).

Dissemination of the process is common and frequently results in involvement of the skin and of the central nervous system (CNS). In the present series, three patients presented cutaneous abscesses and four CNS involvement, and all four died. For one of them (patient 8), even though cerebrospinal fluid (CSF) culture was positive for *Nocardia asteroides*, autopsy revealed only meningoencephalitis due to *Cryptococcus sp*. Two other patients (1 and 4) presented disseminated lesions throughout the CNS and necropsy revealed multiple brain abscesses caused by *Nocardia*. Dissemination to other sites is infrequent [11, 21] and was observed in case 9, whose autopsy revealed pericarditis due to *Nocardia sp* in addtion to pneumonia.

The difficulty in establishing a diagnosis of *Nocardia* infection in immunosuppressed patients has been attributed to several factors. Particulary outstanding

Table 1

General Patient's data

Patient	Sex	Age	Profession	Immunosuppression	Tx-infection interval (months)	Relationship with pulsetherapy (*)
1	F	35	House Wife	A + P	6	No
2	M	33	Brick Layer	A + P + C	2	No
3	M	28	Technician	A + P	2	No
4	F	35	House Wife	A + P	6	No
5	M	19	Factory Worker	A + P	29	Yes
6	M	36	Inactive	A + P	3	No
7	M	35	Butcher	A + P	2	No
8	M	32	Inactive	P + C	28	No
9	M	32	Store Keeper	A + P	48	No

A= Azathioprine P= Prednisone C= Cyclosporine

(*) = Use of high doses of corticosteroids

Table 2

Clinical picture, diagnosis, treatment, and outcome

Patient	Symptoms	Diagnostic Method	Site of Diagnosis	Involved Site	Treatment	Outcome	Autopsy Finding
01	Fever skin absc.,vomiting	Culture	CSF(*1)	Lung,Skin, CNS	Erythrom,oxacil., chloramph.	Death	Multiple lung absces. CNS,Kidney
02	Fever,cough,skin absc.,diarrhea	Culture	Skin Abscess	Lung,Skin	Phosphom.,cloramph., amicacin.		Cure
03	Fever,cough, pleural pain	Culture	Lung,ganglion, biopsy	Lung, ganglion	Cephalothin,amphoter B, SMX-TMP		Cure (2*)
04	Fever,cough, vomiting	Culture	CSF	Lung,CNS	Phosphom,Ampicillin, SMX-TMP	Death	CNS,abcs.,meningitis pneumonia
05	Pleural pain,skin abscess	Autopsy		Lung,skin	Penicillin,Ampicillin	Death	Abscessed bronchopn.
06	Fever,cough, pleural pain	Culture	Pleural lung fluid	Lung	Gentam.,Cephalothin, oxacilin,Amicacin, Amphoter.B, SMX-TMP	Death	Pneumonia,meningitis Criptococcus sp nodules in CNS
07	Fever,cough, diarrhea, vomiting	Autopsy		Lung	Rifocin, Gentam., Metronidaz.,Cephalothin	Death	Abscessed bronchopn.
08	Fever,cough, vomiting	Culture	CSF	Lung	Cephalothin, Chloramph., Ceftriaxonem 5- fluorouracil, SMX-TMP	Death	Aspergillus sp meningitis
09	Fever,cough, diarrhea,pleural pain,vomiting	Autopsy		Lung Pericardium	Amicacin,cephoxitin	Death	Pneumonia Pericarditis

*1: Result obtained on the day of death
*2: Relapse 6 months after the end of treatment

among them are a nonspecific clinical picture, previous use of antibiotics, concomitant infectious processes and the characteristics of the microorganism, which usually presents slow growth in a culture medium [5, 11, 13, 14, 18]. In the present series, the minimun time for bacterial growth in culture was 4 days and the maximun, 40 days. Thus it is imperative not to discard cultures from immunosuppressed patients which show no growth after 48-72 hours, as is usually done.

Although the microorganism is sensitive to many antimicrobial agents such as ampicilin and amicacin [24], minocycline [17], ciprofloxacin, amoxicillin- clavulanate and imipenem [6], the treatment of choice is a association of sulfamethoxazole and trimethoprim (SMX-TMP) [9, 11, 13, 23].

Among the cases reported, patients 2, 3 and 6 responded satisfactorily to treatment. Patient 2, was treated with amicacin and SMX-TMP, and considered to be clinically cured of the infection. He used the medication for one year and then discontinued it; six months later, he suffered a recurrence of infection and was again treated with SMX-TMP, with good results. This case seems to illustrate the need for long-term treatment in order to avoid relapses [23]. Patient 6 was under SMX-TMP therapy when the diagnosis of *Nocardia* infection was confirmed but, after 55 days of the beginning of the treatment he died, due to disseminated *Cryptococcus* infection. Autopsy did not reveal *Nocardia* infection, and doubts remain about its importance as a determinant of the poor course observed.

The mortality of *Nocardia* infection seems to be related with the extent of dissemination of the infection, which frequently occurs as consequence of delay in the diagnosis [1, 7, 12, 16, 18, 23]. In the present series, overall mortality was 77%. In five of the patients who died of *Nocardia* infection the diagnosis was tardy, and for the others three, the diagnosis was accomplished *post mortem*.

On the basis of the above data, we may conclude that *Nocardia* has a good prognosis for renal transplant recipients when diagnosed and treated in time. This requires a high level of awareness with respect to the suspicion of the possibility of *Nocardia* infection,

Table 3

Identification of the microorganism

MATERIAL	Pt.	Staining GRAM	Staining KINYOUM	Culture MEDIUM	UREAS	CASEIN	THYROSINE	XANTHINE	STARCH	GELATIN	DIAGNOSIS
CSF	01	Positive	Positive	ACH+LJ	Positive	Negative	Negative	Negative	Negative	Negative	*N. asteroides*
Skin abscess	02	Positive	Positive	ACH	Positive	Negative	Positive	Negative	Negative	Positive	*N. brasiliensis*
Lung Ganglion	03	Positive	Positive	ACH+ASG + MY	Positive	Negative	Negative	Negative	Negative	Negative	*N. asteroides*
CSF	04	Positive	Positive	ACH+LJ	Positive	Negative	Negative	Negative	Negative	Negative	*N. asteroides*
Pleural effusion	06	Positive	Positive	ACH+LJ	Positive	Negative	Negative	Negative	Negative	Negative	*N. asteroides*
CSF	08	Positive	Positive	ACH	Positive	Negative	Negative	Negative	Negative	Negative	*N. asteroides*

CSF = Cerebrospinal fluid
ACH = Agar chocolate
LJ = Lowentein-Jensen
ASG = Agar Sabouraud Glucose
MY = Mycosel

particularly among patients with pulmonary, neurological or cutaneous involvement.

Clinical aggressive procedures for the detection of the etiological agents are indicated under this circumstances in order to make as early as possible a diagnosis of this potencially fatal infectious complication.

RESUMO

Infecção por *Nocardia* em transplante renal: Considerações diagnósticas e terapêuticas

Foram analisados retrospectivamente 500 prontuários de pacientes transplantados renais no período de 1968 a 1991, sendo identificados 9 casos de Nocardiose; 7 do sexo masculino e 2 do sexo feminino. A idade mediana destes pacientes foi de 33 anos e a infecção ocorreu nos primeiros 6 meses em 6 pacientes, havendo relação direta com pulsoterapia em apenas um paciente. Manifestações pulmonares ocorreram em 100% dos casos, sendo que os sintomas mais frequentes foram febre, tosse e dor pleural. As alterações radiológicas observadas compreenderam infiltrados nodulares em 55% e abcessos em 22% dos casos.

Houve disseminação para a pele em 3 pacientes, para o SNC em 4 pacientes, e 1 paciente apresentou, além de comprometimento pulmonar, pericardite por *Nocardia*.

Em nossa casuística o diagnóstico foi post-mortem em 30% dos casos e a mortalidade foi de 77%. Em 3 pacientes, cujo diagnóstico foi precoce, houve resposta satisfatória ao tratamento instituído.

As infecções por *Nocardia* apresentam bom prognóstico quando diagnosticadas a tempo, sendo portanto necessário um alto grau de suspeição, principalmente em pacientes imunossuprimidos com acometimento pulmonar, neurológico ou cutâneo.

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