

AGREEMENT BETWEEN PREMORTEM AND POSTMORTEM DIAGNOSES IN PATIENTS WITH ACQUIRED IMMUNODEFICIENCY SYNDROME OBSERVED AT A BRAZILIAN TEACHING HOSPITAL

Aécio Sebastião BORGES, Marcelo Simão FERREIRA,
Sérgio de Andrade NISHIOKA, Marco Túlio Alvarenga SILVESTRE, Arnaldo Moreira SILVA & Ademir ROCHA

SUMMARY

Acquired immunodeficiency syndrome (AIDS) is one of the main causes of death in adults worldwide. More commonly than in the general population, in patients with AIDS there is substantial disagreement between causes of death which are clinically suspected and those established by postmortem examination. The findings of 52 postmortem examinations were compared to the premortem (clinical) diagnoses, and there was 46% agreement between them. Fifty two percent of the patients had more than one postmortem diagnosis, and 48% had at least one AIDS-related disease not suspected clinically. Cytomegalovirus infection was the commonest (30.7%) autopsy finding, but not a single case had been suspected premortem. Bacterial infection, tuberculosis, and histoplasmosis were also common, sometimes not previously suspected, postmortem findings. This study shows that multiple infections occur simultaneously in AIDS patients, and that many among them are never suspected before the postmortem examination. These findings suggest that an aggressive investigation of infections and cancers should be done in patients with AIDS, particularly in those who do not respond to therapy of an already recognized condition.

KEYWORDS: AIDS; Necropsy; Opportunistic infections.

INTRODUCTION

Since its recognition in 1981 the acquired immunodeficiency syndrome (AIDS) has become one of the main causes of death, particularly of young adults between 25 and 40 years of age. According to the World Health Organization more than 150 deaths attributed to this disease are estimated to occur daily worldwide^{5,17}.

Important information about opportunistic infections and tumors associated with AIDS has been obtained from postmortem studies, which has increased the understanding of the pathophysiology of this entity^{16,17}. Nevertheless few autopsy studies have been published in the literature, and since the recognition of the syndrome the proportion of postmortem examinations in patients dying with AIDS has declined from 46% to 17% in the United States¹⁶. In Brazil, we are aware of only two published studies addressing autopsy findings in AIDS patients^{2,12}.

In autopsies of AIDS patients there is substantial disagreement between the clinical diagnoses and the postmortem findings^{5,6}. We herein report the findings of 52 autopsies performed in a Brazilian teaching hospital during a 7-year period, and compare them with their premortem diagnoses.

PATIENTS AND METHODS

We reviewed the charts and the autopsy reports of the 52 patients who died with AIDS and had postmortem examination at the teaching hospital of the Federal University of Uberlândia, in Uberlândia, Minas Gerais state, in southeastern Brazil, from January 1989 to January 1996. Data on age, gender, and risk factors to human immunodeficiency virus (HIV) infection, as well as on clinical manifestations and laboratory tests were abstracted. All the patients included in this study fulfilled the criteria for diagnosis of AIDS of the Centers for Disease Control and Prevention, of the United States of America³. Clinical diagnoses included those confirmed by a laboratory test, those

considered as probable due to good response to therapy, and those suspected clinically but unconfirmed. The histopathologic examination of organs and tissues included specific staining for the diagnosis of opportunistic infections, such as Ziehl-Neelsen for mycobacteria, periodic-acid Schiff (PAS) and Gomori-Grocott for fungi, and immunohistochemical techniques for *Trypanosoma cruzi*, *Toxoplasma gondii*, and lymphomas. In 7 of the 52 patients the necroscopic examination was only partial, i.e. did not involve all the organs.

For each patient, we considered that there was agreement between the main clinical and the postmortem diagnoses when both were the same, even if other clinically unsuspected diseases were recognized at autopsy. There was disagreement when the postmortem diagnosis(es) differed from the main clinical diagnosis. Therefore if a patient had a clinical diagnosis of pulmonary tuberculosis, and the postmortem examination revealed pulmonary tuberculosis and adrenal cytomegalovirus, we considered that the diagnoses agreed, and the latter was labeled as an unsuspected infection, whereas if neurotoxoplasmosis was suspected, and the patient died of Chagas' disease encephalitis, the diagnoses disagreed.

Agreement between diagnoses was also looked at independently of the patients, i.e. we calculated the proportion of clinical diagnoses that were confirmed by the postmortem examination.

RESULTS

The age of the 52 cases ranged from 15 and 54 years (mean $33.3 \pm$ standard deviation 9.9; median 32.5); 36 (69.2%) out of them were males, 16 (30.7%) were drug addicts, 9 (17.3%) homosexuals, 6 (11.5%) heterosexuals, 4 (7.7%) homosexual and drug addicts, and 1 (1.9%) hemophiliac. A risk factor for HIV infection was not established in 16 patients (30.7%).

In two out of the seven partial postmortem examinations, there was no evidence of opportunistic infection or neoplasia. These were not included when agreement between pre- and postmortem diagnoses were looked at. The infectious and neoplastic diseases which were diagnosed at autopsy are displayed in table 1.

The agreement between pre- and postmortem diagnoses are shown in table 2. Out of the 50 analyzed patients, 23 had at least one clinical diagnosis which was confirmed by autopsy, i.e. there was agreement of 46%. Twenty-four (48%) patients had at least one AIDS-related disease that was not suspected on clinical grounds. Twenty-six (52%) patients had more than one disease diagnosed at autopsy.

As to the diagnoses, only 27 (30.3%) out of the 89 which were made postmortem were suspected clinically.

Cytomegalovirus (CMV) infection was the commonest autopsy finding. Out of the 16 cases, none had been suspected clinically. In 11 the infection was restricted to the adrenals, in 2

to the adrenals and the intestine, in 1 to the adrenals and the lungs, in 1 to the lungs only, and in 1 to the esophagus.

A systemic mycosis was diagnosed in 16 cases. There were 6 cases of histoplasmosis (4 disseminated, 1 pulmonary, 1 intestinal), 6 cases of cryptococcosis (4 disseminated, 1 involving the central nervous system – CNS –, 1 pulmonary – in the latter case postmortem examination of the CNS was not done), and 4 cases of candidiasis (3 esophageal, 1 pulmonary). Out of the 6 cases of cryptococcosis, 5 were diagnosed premortem.

Out of the 11 cases of toxoplasmosis found at autopsy, 9 involved the CNS only, 1 the CNS and the esophagus, and there was 1 case of disseminated disease, involving pancreas, adrenals, ovaries, stomach, intestines and CNS. Clinical diagnosis had been done in only 5 of these cases, all of them with infection restricted to the CNS.

Nine patients had a disseminated mycobacterial infection; 3 of them were suspected clinically. Out of the 3 cases of reactivation of Chagas' disease, 1 had myocarditis and meningoencephalitis, 1 myocarditis only (CNS not examined), and 1 meningoencephalitis only (only the CNS was examined). A neoplastic disease was detected in 5 cases, 3 of them with disseminated lymphoma (1 Hodgkin, 1 pleomorphic large cell T-cell lymphoma, and 1 centroblastic-centrocytic lymphoma), 1 with an adenocarcinoma of the small bowel and 1 with Kaposi sarcoma involving skin, liver, lungs, pleura, lymphnodes, spleen, stomach and pancreas.

DISCUSSION

Autopsies remain important nowadays for the study of infectious diseases, having a significant role for the understanding of the epidemiology, pathophysiology and diagnosis of diseases such as AIDS, and emergent infections such as those caused by arenaviruses, Ebola virus and hantaviruses, notwithstanding the progresses in the laboratory diagnoses *in vivo*^{7,10,13}.

GOLDMAN et al.⁴, studying the importance of autopsies in the recognition of infectious diseases in the general population, found that 24% of the postmortem diagnoses were either misdiagnosed or not recognized clinically. In a study not restricted to infectious diseases, CAMERON & McGOOGAN¹ found 72% of disagreement between clinical and postmortem diagnoses. HUI et al.⁵ found 15 infections or neoplasms not previously recognized in autopsies of 10 out of 12 patients with AIDS, and WILKES et al.¹⁷ found that 74% of AIDS-related diseases had not been diagnosed clinically.

In this study we found that the agreement between clinical and postmortem diagnoses was achieved in only 46% of the patients, and in 30% of the total number of postmortem diagnoses. Cytomegalovirus and bacterial infections were the most prevalent, having been seen more often than other diseases perceived as common among patients with AIDS, such as

TABLE 1
Infectious and neoplastic diseases diagnosed at postmortem examination of 52 patients with AIDS

Disease	Nº of diagnoses	Proportion among the 52 cases (%)
Cytomegalovirus (CMV) infection	16	30.7
Bacterial infection	16	30.7
Toxoplasmosis	11	21.2
Tuberculosis	9	17.3
Histoplasmosis	6	11.5
Cryptococcosis	6	11.5
Pneumocystosis	5	9.6
Candidiasis	4	7.7
Reactivated Chagas' disease	3	5.8
Lymphoma	3	5.8
Necrotizing encephalitis (*)	3	5.8
Systemic strongyloidiasis	2	3.8
Kaposi's sarcoma	1	1.9
Herpes simplex	1	1.9
Intestinal adenocarcinoma	1	1.9
Vacuolar myelopathy	1	1.9
Encephalitis – unspecified	1	1.9

(*) unknown cause

TABLE 2
Agreement between antemortem and postmortem diagnoses in 50 patients with AIDS (number of cases)

Disease	Clinical diagnosis		Postmortem diagnosis		Total
	suspected	confirmed	previously suspected	previously unsuspected	
CMV infection	1	0	0	16	16
Bacterial infection	20	9	6	10	16
Toxoplasmosis	12	2	5	6	11
Tuberculosis	14	1	3	6	9
Histoplasmosis	2	2	1	5	6
Cryptococcosis	5	5	5	1	6
Pneumocystosis	11	2	2	3	5
Candidiasis	2	2	1	3	4
Chagas' disease	5	3	1	2	3
Lymphoma	1	0	1	2	3
Necrotizing encephalitis	0	0	0	3	3
Strongyloidiasis	2	2	1	1	2
Kaposi's sarcoma	1	0	1	0	1
Herpes simplex	0	0	0	1	1
Intestinal adenocarcinoma	0	0	0	1	1
Vacuolar myelopathy	1	0	1	0	1
Encephalitis – unspecified	0	0	0	1	1

Pneumocystis carinii infection. One likely explanation for the low prevalence of *P. carinii* infection at autopsy is the common use of primary and secondary prophylaxis against this agent in patients with HIV infection, that has led it to become a less important cause of death among these individuals.

Cytomegalovirus infection was the commonest postmortem diagnosis in this study, a finding that has also been reported in the literature^{8,14}. Nineteen percent of our cases presented a disseminated infection, but in none the diagnosis was suspected

premortem, probably due to the lack of specific symptoms and to the fact that the diagnosis depends mostly of histopathologic examination.

Tuberculosis remains among the commonest opportunistic infections, and is one of the leading causes of death in patients with AIDS. Very often the clinical diagnosis of tuberculosis in these patients is not well defined because of its atypical presentation, sometimes severe, for instance mimicking a Gram negative sepsis. In

this study the diagnosis of tuberculosis was suspected on clinical grounds in only 33.3% of the time, and in only 11.1% it was confirmed premortem, findings which were consistent with those of other series^{9,14,15,16}.

It is of interest the presence in this series of cases of parasitic diseases which are endemic in our region, such as strongyloidiasis and Chagas' disease. We identified by postmortem examination 3 cases of reactivation of Chagas' disease in patients who had clinical, laboratory and/or radiological manifestations of meningoencephalitis and/or myocarditis, all of them mistakenly diagnosed and initially treated for neurotoxoplasmosis. Two other cases had the diagnosis of reactivation suspected clinically, confirmed by isolation of trypanomastigote forms of the parasite in the blood or cerebrospinal fluid, and received early treatment. One of them survived a few months, died of sepsis, and had no evidence of the disease at the postmortem examination, what was interpreted as an evidence that the therapy was effective¹¹. Two cases of overwhelming strongyloidiasis were found in this study, but only one was diagnosed and treated premortem.

The occurrence of disseminated fungal infections in AIDS patients is high, and so is their case-fatality rate^{5,6,7}. In 30.7% of the autopsies of this study there was a deep fungal infection, either histoplasmosis, cryptococcosis or candidiasis, 56.3% of them not suspected clinically. There was no case of the commonest deep mycosis in our region, paracoccidioidomycosis, possibly because *Paracoccidioides brasiliensis*, the agent of this disease is sensitive to sulfonamides and azoles, drugs that are commonly used for the treatment and prophylaxis of other opportunistic infections in AIDS patients¹⁰.

Toxoplasmosis was ranked third in frequency in this series, being diagnosed in 21.2% of the cases, about one fifth of them with generalized disease not suspected clinically. Kaposi's sarcoma was found in only one patient in this series, possibly because the cutaneous manifestations of this disease are easily diagnosed, and therefore postmortem examination is seldom performed in these patients. The 3 cases of necrotizing encephalitis of unknown etiology could possibly be cases of partially treated *T. gondii* encephalitis, or the etiologic diagnosis was not made due to the lack of sensitivity of the diagnostic techniques.

Studies involving postmortem examinations do not measure the prevalence of opportunistic infections and cancers among HIV infected individuals. The highly prevalent infections are more likely to be diagnosed and treated, or even to be treated empirically. Studies such as ours do show, however, that multiple opportunistic infections occur simultaneously in patients with AIDS, and that many of them remain undetected, eventually contributing to the death of these individuals. This finding teaches us that aggressive investigation of infections and cancers should be done in patients with AIDS, particularly those who do not respond to therapy of an already recognized condition.

RESUMO

Concordância entre diagnósticos clínicos e de necrópsia em pacientes com síndrome da imunodeficiência adquirida observados em um hospital universitário brasileiro

A síndrome da imunodeficiência adquirida (SIDA) é uma das principais causas de morte em adultos em todo mundo. Com maior frequência do que ocorre na população geral, há em pacientes com SIDA uma substancial discordância entre as causas de morte clinicamente suspeitadas e as estabelecidas pelas autópsias. Revisamos os achados de 52 necrópsias de pacientes com SIDA e seus respectivos diagnósticos clínicos, e encontramos 46% de concordância entre eles. Cinquenta e dois por cento dos pacientes tiveram mais de um diagnóstico necroscopicamente definido e 48% tiveram pelo menos uma doença relacionada à SIDA, não suspeitada clinicamente. Infecção pelo citomegalovírus foi o achado necroscópico mais comum (30,7%) e em nenhum dos casos o diagnóstico foi suspeitado em vida. Infecção bacteriana, tuberculose, e histoplasmoze foram também achados freqüentes de necrópsia, por vezes não suspeitados anteriormente. Este estudo demonstra que múltiplas infecções ocorrem simultaneamente em pacientes com SIDA, sendo que muitas delas sequer são suspeitadas clinicamente. Estes achados sugerem que investigação agressiva de infecções e neoplasias deva ser feita em pacientes com SIDA, particularmente naqueles que não respondem ao tratamento de uma patologia já diagnosticada.

REFERENCES

1. CAMERON, H.M. & McGOOGAN, E. – A prospective study of 1152 hospital autopsies: analysis of inaccuracies in clinical diagnoses and their significance. *J. Path.*, 133:285-300, 1981.
2. CARVALHO, M.G.F.; RODRIGUES, M.A.M.; MARQUES, M.E.; FRANCO, M. & MONTENEGRO, M.R. – Lesões do trato gastrointestinal na síndrome da imunodeficiência adquirida: estudo de 45 necrópsias consecutivas. *Rev. Soc. bras. Med. trop.*, 27:135-141, 1994.
3. CENTERS FOR DISEASE CONTROL – Revision of the case definition of acquired immunodeficiency syndrome for national reporting – United States. *MMWR*, 34:373-375, 1985.
4. GOLDMAN, L.; SAYSOM, R.; ROBBINS, S. et al. – The value of the autopsy in three medical eras. *New Engl. J. Med.*, 308:1000-1005, 1983.
5. HUI, A.N.; KOSS, M.N. & MEYER, P.R. – Necropsy findings in acquired immunodeficiency syndrome: a comparison of premortem diagnoses with postmortem findings. *Hum. Path.*, 15:670-676, 1984.
6. KLATT, E.C.; NICHOLS, L. & NOGUCHI, T.T. – Evolving trends revealed by autopsies of patients with the acquired immunodeficiency syndrome. *Arch. Path. Lab. Med.*, 118:884-890, 1994.
7. LYON, R.; HAQUE, A.K.; ASMUTH, D.M. & WOODS, G.L. – Changing patterns of infections in patients with AIDS: a study of 279 autopsies of prison inmates and nonincarcerated patients at a university hospital in eastern Texas, 1984-1993. *Clin. infect. Dis.*, 23:241-247, 1996.
8. MORGELL, S.; CHO, E-S.; NIELSEN, S.; DEVINSKY, O. & PETITO, C.K. – Cytomegalovirus encephalitis in patients with acquired immunodeficiency syndrome: an autopsy study of 30 cases and a review of the literature. *Hum. Path.*, 18:289-297, 1987.
9. NIETD, G.W. & SCHINELLA, R.A. – Acquired immunodeficiency syndrome: clinicopathologic study of 56 autopsies. *Arch. Path. Lab. Med.*, 109:727-734, 1985.

10. NISHIOKA, S.A. – Paracoccidioidomycosis and AIDS. **Clin. infect. Dis.**, **22**:1132, 1996.
11. NISHIOKA, S.A.; FERREIRA, M.S.; ROCHA, A. et al. – Reactivation of Chagas' disease successfully treated with benznidazole in a patient with acquired immunodeficiency syndrome. **Mem. Inst. Oswaldo Cruz**, **88**:493-496, 1993.
12. OKOSHI, M.P. & MONTENEGRO, M.R. – Patologia do coração na AIDS: estudo de 73 necrópsias consecutivas. **Arq. bras. Cardiol.**, **66**:129-133, 1996.
13. SCHWARTZ, D.A. & HERMAN, C.J. – Editorial response: the importance of the autopsy in emerging and reemerging diseases. **Clin. infect. Dis.**, **23**:248-254, 1996.
14. STEVANOVIC, G.; TUCAKOVIC, G.; DOTLIC, R. & KANJUH, V. – Correlation of clinical diagnoses with autopsy findings. **Hum. Path.**, **17**:1225-1230, 1986.
15. SUNDERAN, G.; McDONALD, R.J.; MANIATIS, T. et al. – Tuberculosis as a manifestation of the acquired immunodeficiency syndrome. **J. Amer. med. Ass.**, **256**:362-366, 1986.
16. WILKES, M.S.; FELIX, J.C.; FORTIN, A.H.; GODWIN, T.A. & THOMPSON, W.G. – Value of necropsy in acquired immunodeficiency syndrome. **Lancet**, **9**:85-88, 1988.
17. WILKES, M.S.; JACOBS, T.A.; MILBERG, J. & STONEBURNER, R. – Autopsy patterns in patients dying of acquired immunodeficiency syndrome in New York City. **Arch. Pat. Lab. Med.**, **112**:1221-1223, 1988.

Recebido para publicação em 14/04/1997

Aceito para publicação em 27/08/1997

