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Galactomannan as a Diagnostic Test for Invasive Pulmonary Aspergillosis in a Patient with Primary Immunodeficiency: Case Report

Moreno-Miceli Miguel[1], Ordoñez-Rodríguez Tatiana[2], Ramírez-Ruiz Antonio[3], Rodríguez-Relingh Kim[4], Romero-Sánchez Alan Jesús[5], Cabrera-Moreno María Indalecia[6], Quiñones-Martinez Mayra Evelyn[7]

[1,2,3,4,5,6,7] Instituto Mexicano del Seguro Social, Unidad Medica de Alta Especialidad No. 14 Veracruz, Hospital de Alta Especialidad de Veracruz.

https://orcid.org/0009-0006-7636-6983[4]

ABSTRACT

Introduction: Aspergillosis continues to be the most frequent fungal infection in the hematopoietic stem cell transplanted patient, however, in other types of immunocompromised states, such as primary immunodeficiencies, are scarce. Therefore, many times the diagnosis of invasive aspergillosis is often a diagnostic challenge for the clinician, so we highlight the usefulness of galactomannan in immunocompromised patients for the diagnosis of aspergillosis.

Background: Invasive aspergillosis together with chronic pulmonary aspergillosis and allergic bronchopulmonary aspergillosis, constitute the clinical forms of aspergillosis. Aspergillus fumigatus-complex is the most frequent etiological agent, the increase in immunosuppressive treatments and the greater use of corticoids have led to a greater prominence of aspergillosis in recent years. The use of galactomannan and imaging tests complement the microbiological limitations in the diagnosis of these patients, the mortality of invasive forms depends on the clinical form and the type of host.

Objective: To demonstrate the importance of galactomannan as a noninvasive diagnostic test for invasive pulmonary aspergillosis, in centers with limited resources where it is not possible to perform a histopathological study.

Case presentation: We present the case of an 18-year-old male patient with immunodeficiency due to T lymphocyte immunoregulation dysfunction, who developed invasive pulmonary aspergillosis with a positive galactomannan test.

Conclusions: Our case report reflects the diagnosis of ante-mortem invasive pulmonary aspergillosis in an adult patient with primary T-lymphocyte immunodeficiency, non-neutropenic, in whom a histopathological study to optimize the diagnosis was not possible, and whose only tool we had was the measurement of GM.

Abbreviations: GM= Galactomannan

KEYWORDS: Case report, galactomannan, aspergillosis, aspergillus coindia, invasive pulmonary aspergillosis, primary immunodeficiency.

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INTRODUCTION

Aspergillosis comprises a spectrum of clinical scenarios secondary to inhalation or inoculation of the fungus Aspergillus conidia. The various phenotypes of the disease are largely dependent on host factors, predominantly the immune response to infection. The disease manifests as clinical syndromes classified as non-invasive, e.g. bronchopulmonary aspergillosis and allergic fungal rhinusitis, invasive forms include chronic pulmonary aspergillosis and invasive pulmonary aspergillosis(1).

Aspergillosis remains the most common fungal infection in the hematopoietic stem cell transplant recipient (2). However, the overall evidence regarding the management of aspergillosis in other types of immunocompromised states, such as primary immunodeficiencies, is sparse.

Here, we present a case report of a young adult with primary T-lymphocyte immunodeficiency in whom the diagnosis of

disseminated aspergillosis was integrated by a noninvasive method.

PRESENTATION OF THE CASE

We present the case of an 18 year old patient, with the following important antecedents: Immunodeficiency due to immunoregulation dysfunction in T lymphocytes, 4 years of diagnosis, in previous treatment with immunoglobulin. Autoimmune thrombocytopenic purpura of 1 year of diagnosis, in treatment with Prednisone 5 mg every 24 hours. Surgical: Splenectomy in 2019 due to splenic abscess, with development of hemoperitoneum and subsequent perforation of the transverse colon, requiring primary closure with reoperation for peritonitis, ileostomy with shunt was performed, developing enterocutaneous fistula, with placement of VAC system on 07.05.2021. Infectious: Dengue in 2014. Chikungunya in 2017, recurrent respiratory tract infections, with 4 previous hospitalizations for pneumonia, last picture in November 2022.

She started on 03/03/23 with increase in enterocutaneous fistula output, with purulent discharge and hematic debris, adding dyspnea Borg 8/10 and palpitations. Physical examination: neurologically intact, auscultation integrates bilateral consolidation syndrome, tachycardic, with presence of enterocutaneous fistula with serohematic drainage of 100 ml. Laboratory studies were requested as shown in the first column of table 1, peripheral blood culture, urine culture and enterocutaneous fistula secretion culture were sent.

Chest-abdominal CT scan with bilateral basal consolidations with right atelectasis, with suspicion of aggregate pneumonic process, scarce perihepatic fluid, presence of known enterocutaneous fistula.

Rapid test against Sars-Cov2 was negative, antimicrobial management with ceftriaxone and Metronidazole was started. Evolving with low output data, requiring vasopressor, assessed by allergology indicating management with immunoglobulin 800 mg/kg/dose, due to data of septic shock of pulmonary focus, SAPS II 31 points, APACHE II 6 points, SOFA of 12 points (mortality 40-50%), antibiotic treatment was escalated to Meropenem and admission to ICU on 07. 03.03.23, assessed by infectious diseases, with suspicion of encapsulated pathogens, atypical and fungi due to immunosuppression, management with moxifloxacin and Voriconazole was added, requesting expectoration culture of atypical bacteria and fungi, urinary antigen, etc.

of Legionella and galactomannan. Evaluated by Hematology on 08/03/23 for a history of immune thrombocytopenia, suspending steroid treatment. He was readmitted to Internal Medicine on 09.03.23 preceded by ICU, with persistence and progression of dyspnea Borg 4-8/10, clinically with use of accessory musculature and desaturation of 84%, despite the reservoir mask at 15/l minute, deciding on advanced airway management and return to ICU, 12. 03.03.23, maintained with AMV within alveolar protection parameters, started Weaning protocol, failing in tests, 13.03.23 reevaluated by infectology, with severe lymphopenia initiating coverage with trimethoprim-sulfamethoxazole, 14.03. 23 presented with decreased urinary flow up to 0.38 ml/kg, presenting with AKI, renal USG with finding of acute left pyelonephritis, with perirenal collection, management was optimized with crystalloid solutions, improving urinary output to 0.5 ml/kg, 15.03. Ultrasound was performed documenting diaphragmatic dysfunction, presenting increased transaerial pressure, tomography showed decreased lumen of orotracheal cannula, warranting change, galactomannan of 1.57 (positive) was collected, confirming invasive aspergillosis. Tracheostomy was performed on 19.03.23, reevaluated by allergology, indicating a new dose of immunoglobulin, urine culture, aerobic CVC blood culture and aerobic peripheral blood culture without development after 7 days were reported On 17.03.23 a culture of secretion of enterocutaneous fistula was collected, with development of Candida tropicalis sensitive to voriconazole, so the established management was continued.

20.03.23 with a procalcitonin report of 0.56, complying with the 14-day meropenem scheme, suspension was indicated. 22.03.23 vasopressor was withdrawn with TAM of 71 mm Hg, moxifloxacin was suspended. 24.03.23 jaundice was documented, cholestatic pattern was highlighted in paraclinics, USG of liver and biliary tract was requested, with report of subhepatic collection of 4.8 cc, ruling out obstructive process, suspecting hepatic dysfunction associated to septic shock. He was discharged to internal medicine again to complete the antifungal regimen. On 03.25.23 he had a torpid evolution, leading him to shock, vasopressor was restarted, requiring mechanical ventilation again, with FIO2 at 100%, without achieving SAO2 greater than 90%, gasometrically with severe metabolic acidosis refractory to treatment, leading him to cardio-respiratory arrest on the 26th. 03.03.23 at 10:17 hours, confirming asystole by monitor, cardiopulmonary resuscitation maneuvers were started, without achieving return to spontaneous circulation, declaring time of death at 10:27 hours on 26.03.23

CASE DISCUSSION

Invasive pulmonary aspergillosis is increasingly being recognized as a highly prevalent entity in critically ill patients. In addition to recognizing the higher prevalence of the disease in patients with hematologic malignancies and hematopoietic stem cell transplant (HSCT) recipients, a higher incidence has now been observed in those individuals with particular comorbidities, such as chronic obstructive pulmonary disease, cirrhosis, previous Covid infection or influenza. In these types of cases, grouped as non-neutropenic patients, the clinical features and radiological findings are more insidious, and therefore represent a greater diagnostic

challenge for the clinician. This situation becomes apparent through comparative studies of postmortem patients, in which it has been observed that one of the most frequently missed diagnoses is aspergillosis. Roosen et al. conducted a retrospective comparative study on patients in the intensive care unit, with the aim of investigating whether the performance of postmortem autopsies has an educational and clinical utility over premortem clinical diagnosis.

One of the most important results is that of the 100% of postmortem diagnoses, 16% represented major diagnoses that could have generated a change in therapy and possibly prolonged survival, among which aspergillosis stood out(3). Tejerina et al. conducted a similar retrospective study in which they analyzed postmortem diagnoses obtained through autopsies performed in the intensive care unit over a period of 25 years, in this study 893 autopsies were included. Among its results, of the 100% (n=893) of the postmortem examinations, 2.8% (n=25) resulted in a diagnosis of invasive pulmonary aspergillosis, of which only 40% (n=10) of the diagnoses were made ante-mortem(4).

Although there is a consensus on the definition of aspergillosis for diagnostic, therapeutic and research purposes by the National Institute of Allergy and the Mycosis and Infectious Diseases Study Group (EORTC/MSG), its applicability is largely restricted to patients with a certain immunocompromised phenotype, since when applying the algorithm (in the absence of the gold standard method) to patients in the intensive care unit, up to 84% of cases fail to be classified(5,6).

Given the clinical challenge and the difficulties involved in making a confirmatory diagnosis through histopathological study in centers with limited resources, the use of non-invasive tests for the diagnosis of aspergillosis in daily medical practice has become more important. The AspICU study was initially conducted by Blot et al. with the aim of developing a diagnostic definition that would have greater applicability for the diagnosis of aspergillosis in the intensive care unit. The original study proposed a positive culture as an entry criterion for the diagnosis of aspergillosis. Given the evidence of negative culture results in the vast majority of reported cases, a modification of the criteria was decided by Schauwvlieghe et al. eliminating the requirement for a culture and incorporating galactomannan (GM) as a sufficient mycological criterion for the diagnosis of IPA (7,8). To date, there are several methods to test for GM, either by serum or by bronchoalveolar lavage fluid (BALF). In general, the most recent evidence points to a higher sensitivity and specificity for the diagnosis of aspergillosis from a BALF sample compared to a serum sample.

According to a Cochrane review, the sensitivity and specificity of GM in immunocompromised patients for the diagnosis of aspergillosis is 82% and 81%, respectively (9-12). It is important to note that the initial studies carried out for the proposals for the operational definition of aspergillosis diagnosis were based on samples from patients with hematological malignancies and HSCT recipients; AspICU generated a radical change by integrating new susceptible population groups, in which critically ill patients with influenza virus are included in the sample. The current unanswered question is whether the performance of GM measurement in its various methodologies has a greater diagnostic efficacy according to the type of immunocompromise.

Our case report reflects the diagnosis of IPA in an adult patient with primary T-lymphocyte immunodeficiency, non-neutropenic, in whom histopathology to optimize the diagnosis was not possible, and whose only tool available to us was the measurement of GM, which was positive. We understand the limitations of the test, however, it is of interest to continue identifying the phenotypes of patients in whom the test may be of greater utility, beyond the subgroups of patients with hematologic malignancies and HSCT recipients within the intensive care unit and hospitalization.

	TABLE 1					
	06.03.23	10.03.23	13.03.23	15.03.23	24.03.23	26.03.23
HB	10.7	9.2	8.4	8.4	8	8.3
HTO	33.6	28	26.3	25.8	25.6	27.7
LEU	12.54	10.84	10.78	13.9	9.07	15.73
NEU	10.27	8.27	8.43	11.27	7.87	14.19
LINF	1.88	1.31	1.11	0.96	0.42	0.38
PLAQ	179	343	271	363	273	383
GLU	22	62	68	85	63	43
UREA	49.22	59.92	49.22	47.08	32.1	36.38
BUN	23	28	23	22	15	17
CR	1.65	1.11	1.01	0.86	0.51	0.71
NA	137	141	143	144	137	141
K	4.4	3.8	3.7	4.1	3.9	5.2
CL	100	109	110	110	105	111
BT	1.4	0.9			5.7	
BD	0.9	0.5			4.6	
BI	0.5	0.4			1.1	

AST	47				116	
ALT	45				52	
DHL	226	166			219	
TP	13.4				11.3	
TTP	39.1				38.8	
INR	1.18				1	
ALB		1.6				
CR ORINE		38.02				
PROTEIN 24 HRS		309.1				
PCR			18.5			
GALACTOMANNAN				1.57		

CONCLUSION

During the last decade, the prevalence of fungal infections has been steadily increasing, mainly due to the increase in immunocompromised patients, the widespread use of antimicrobials and the increased use of immunosuppressants, invasive diagnostic maneuvers and implementation of parenteral feeding. Species of the genus Aspergillus are currently the leading cause of invasive fungal disease.

IA is an important infectious cause of morbidity and mortality, the clinical presentation of IA is variable, non-specific and late, being essential to suspect it in risk situations. The most frequent local clinical forms of IA occur in the pulmonary and paranasal sinuses.

The diagnosis of this entity continues to be difficult in non-neutropenic patients, due to the low specificity of the clinical manifestations, and in some cases, the lack of pathognomonic radiological findings, representing a major diagnostic challenge. With the aim of improving and advancing the diagnosis in order to establish a directed antifungal treatment, which allows reducing the mortality associated with IPA, alternative serological techniques to culture have been developed based on the detection of antigens such as the cellular polysaccharide called galactomannan (GM) contributing to the early diagnosis of IA, presenting a very acceptable sensitivity and specificity, in addition to the fact that its levels seem to have prognostic significance, with a decrease in these levels after the initiation of antifungal therapy.

Thus, the measurement of GM represents a noninvasive test of high value for diagnostic confirmation of IPA in centers with limited resources, in patients in whom it was not possible to perform a histopathological diagnosis, allowing early initiation of a targeted antifungal therapy, with the aim of reducing the mortality associated with IPA, however, it is of interest to continue identifying the phenotypes of patients in whom the test may be of greater utility.

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