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RESEARCH ARTICLE

INVASIVE FUNGAL INFECTIONS IN COVID-19 PATIENTS IN THE INTENSIVE CARE UNIT: ABOUT 5 CASES

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Abstract

Covid-19 is a serious pathology; it is associated with a deep immunodepression which favors invasive fungal infections especially in patients in intensive care unit. We report in our work a series of five covid-19 patients with fungal co-infection. We conducted a retrospective study including all COVID-19 patients hospitalized in intensive care unit for acute respiratory distress syndrome. Patients who presented a clinical worsening during their hospitalization were sampled with mycological study (bronchoalveolar lavage, serum and fungal blood culture). The diagnosis of fungal superinfection was retained in five patients, two of whom had probable invasive pulmonary aspergillosis. Two other patients had a *Cryptococcus neoformans* infection, one of which was disseminated. *Candida albicans* sepsis was found in only one patient. In the literature, invasive candidiasis and invasive pulmonary aspergillosis. in covid-19 patients are associated with a high morbidity and mortality rate, hence the importance of early diagnosis and management. It should be noted that the clinical presentation of invasive fungal infections is not very specific, especially at the beginning of the infection when antifungal treatment is more effective.

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Introduction:-

SARS-Cov-2 disease is a new respiratory infectious pathology responsible for a global pandemic. In Morocco, the first case was recorded on March 2, 2020 and since then the intensive care unit in our hospital has experienced a high number of hospitalizations. Covid-19 is a serious pathology; it is associated with a deep immunodepression which favors invasive fungal infections especially in patients in intensive care unit (1) We report in our work a series of 5 covid-19 patients with fungal co-infection.

Patients And Methods:-

We conducted a retrospective, observational study including all COVID-19 patients (positive respiratory CRP to SARS-CoV-2 or compatible thoracic CT-scan results) hospitalized in intensive care unit for acute respiratory distress syndrome (ARDS) between March 15, 2020 and January 1, 2021. Patients who presented a clinical

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worsening during their hospitalization were sampled with mycological study (Bronchoalveolar lavage (BAL), serum and fungal blood culture).

On the BAL samples, we performed:

- Direct examination in the fresh state
- Direct examination after special staining: Indian ink stain, MGG and Zeihl Nelson
- A culture on Sabouraud and Sabouraud medium with added chloramphenicol.
- Complemented by a search for mannan and galactomannan antigen in serum or BAL by ELISA method.

Blood culture samples were incubated at 37°C in BACT/ALERT 3D. The identification of fungi after positivity was done by API 20C AUX gallery.

Results:-

During the study period 157 patients were hospitalized in the intensive care unit, 17 of who presented a clinical worsening during their hospitalization were sampled with mycological study (Table 1). The diagnosis of fungal co-infection was retained in 5/17. The average age of the five patients was 60 years and they were all male.

Two patients presented with probable invasive pulmonary aspergillosis (IPA) according to the diagnostic criteria of the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG). The diagnosis was based on the positivity of BAL cultures for *Aspergillusfumigatus* in first patient and *Aspergillusnidulans* in the second. In addition, serum galactomannan antigen was positive in the first patient only. (Table 1)

Cryptococcusneoformans infection was concluded for two other patients. One had disseminated *Cryptococcus* diagnosed on blood culture and BAL, and the other was isolated on BAL only. Both patients are diabetic and received prolonged corticosteroid therapy for covid 19 during their hospitalization. (Table 1)

Candida albicans sepsis was found in one patient with a positive culture and a positive serum mannan antigen assay. This patient had no previous chronic immunosuppression.

A probabilistic treatment was started after taking samples for the 5 patients with fluconazole adapted according to the results of the mycological study. Mortality was high in our patients with invasive fungal infections (N= 4/5), i.e. 80%.

Discussion:-

Many authors have reported a high frequency of invasive fungal infections in severe forms of COVID-19 in the ICU setting including invasive pulmonary aspergillosis (IPA) (2) . Case series published in Pakistan (3), France (2) and the Netherlands (4) have found a frequency of IPA in COVID-19 patients in the ICU setting of 21.7%, 30% and 19.4% respectively . This high prevalence can be explained by the impaired immune defenses during SARS-CoV-2 infection (5) Also the anti-inflammatory treatments used in covid 19 disease and which aim to control the inflammatory cascade are an additional risk factor for invasive fungal infections(1). In addition to these factors, comorbidities and underlying diseases such as diabetes and hemodialysis are factors in the occurrence of severe forms of covid 19 disease and deep mycoses (6) . Paradoxically to all these studies, it has been reported in France by Saint Leger et al a prevalence of IPA in covid 19 patients comparable to that of IPA in non-COVID-19 ARDS population already described in the literature (7).

Unlike the majority of studies published in the literature, we found a relatively low frequency of IPA (1.27%), which can be explained by the fact that samples were only taken from patients presenting a clinical worsening.

Several species of the genus *Candida* are commensal of the genital and digestive tract of humans, but in case of immune system failure become pathogenic and lead to invasive mycoses of dreadful prognosis. Indeed, candidemia is the fourth most common cause of nosocomial infection in intensive care unit (8). In the case of COVID-19, the wide use of antibiotics, corticosteroids and central venous catheters, as well as the damage caused by SARS-CoV-2 in patients with ARDS, seem to favor the occurrence of candidemias. A study conducted in NEWARK reported a candidemia frequency of 8.9% in covid-19 patients hospitalized in ICU (9). According to a review of the literature,

several cases of invasive candidiasis have been published: Spain (N=3), Italy (N=3), Oman (N=5), India (N=15) with *C. albicans* as the most common species followed by *C. auris*, *C. glabrata* and *C. tropicalis*(8).

Disseminated *Cryptococcus* infections are common in immunocompromised patients and rarely in the immunocompetent(Masson, s. d, 2020). In our study 2 cases of *cryptococcus* infection were diagnosed, one of which was disseminated. To the best of our knowledge, we report the second case of *cryptococcosis* published so far in the literature((10).As we have already detailed the Covid-19 is accompanied by an immune alteration which can explain the occurrence of these opportunistic infections.

The evolution was unfavorable for 4 of our patients, i.e. a mortality rate of 80% despite the introduction of antifungal treatments. In the literature, invasive candidiasis and IPA in covid-19 patients are associated with a high morbidity and mortality rate (1), hence the importance of early diagnosis and management. It should be noted that the clinical presentation of invasive fungal infections is not very specific, especially at the beginning of the infection when antifungal treatment is more effective. For this reason, some authors have suggested that screening covid-19 patients in the ICU setting for IFA could improve their prognosis (11).

Conclusion:-

Our study is the second in the literature to report a case of disseminated *cryptococcosis* in a covid-19 patient in an intensive care unit. This opportunistic infection with the other invasive fungal infections are responsible for a very important mortality rate, hence the interest of a systematic screening and an early treatment. These results must be confirmed by a larger prospective study.

Table 1:- Demographic and clinical characteristics of patients.

Age and gender	M, 64	M, 58	M, 65	M, 65	M, 68
Medical history	-Type 2 diabetes -Smoking	-Type 2 diabetes -Co-infection with - <i>acinetobacter-baumannii</i>	None	-High blood pressure -Type 2 diabetes Smoking	-High blood pressure -Hemodialysis
CLINICAL					
Increased oxygen requirements	+	+	+	+	+
Fever	+	+	+	-	+
Expectorant cough or cough modification	-	-	+	-	-
Sepsis	+	-	-	-	+
MYCOLOGICAL DIAGNOSIS					
Sample site	Blood culture/ BAL	BAL	BAL	BAL	Blood culture
Direct examination	Direct examination with indian ink +	Direct examination with indian ink +	Positive : Presence of septate mycelial filaments at acute angle	Positive : Presence of septate mycelial filaments at acute angle	Positive
Culture	<i>Cryptococcus neoformans</i>	<i>Cryptococcus neoformans</i>	<i>Aspergillus fumigatus</i>	<i>Aspergillus nidulans</i>	<i>Candida albicans</i>
Ag research on BAL /serum	-	-	<i>Galactomannan</i>	-	<i>Mannane</i>
Evolution	Deaths	Deaths	Deaths	Deaths	Good clinical course

References:-

1. Segrelles-Calvo G, de S Araújo GR, Frases S. Systemic mycoses: a potential alert for complications in COVID-19 patients. *Future Microbiology*. sept 2020;15(14):1405-13.
2. Alanio A, Dellièrè S, Fodil S, Bretagne S, Mégarbane B. Prevalence of putative invasive pulmonary aspergillosis in critically ill patients with COVID-19. *The Lancet Respiratory Medicine*. juin 2020;8(6):e48-9.
3. Nasir N, Farooqi J, Mahmood SF, Jabeen K. COVID-19-associated pulmonary aspergillosis (CAPA) in patients admitted with severe COVID-19 pneumonia: An observational study from Pakistan. *Mycoses*. 2020;63(8):766-70.
4. van Arkel ALE, Rijpstra TA, Belderbos HNA, van Wijngaarden P, Verweij PE, Bentvelsen RG. COVID-19-associated Pulmonary Aspergillosis. *Am J Respir Crit Care Med*. 1 juill 2020;202(1):132-5.
5. Wang M, Wu Q, Xu W, Qiao B, Wang J, Zheng H, et al. Clinical diagnosis of 8274 samples with 2019-novel coronavirus in Wuhan. *medRxiv*. 18 févr 2020;2020.02.12.20022327.
6. Eggimann P, Garbino J, Pittet D. Epidemiology of *Candida* species infections in critically ill non-immunosuppressed patients. *Lancet Infect Dis*. nov 2003;3(11):685-702.
7. Saint Leger P, Zarrougui W, Sedrati F, Lambiotte F, El Beki N. Aspergillose pulmonaire invasive chez les patients avec formes sévères de COVID-19 : résultats d'une cohorte monocentrique française. *Med Mal Infect*. sept 2020;50(6):S86.
8. Arastehfar A, Carvalho A, Nguyen MH, Hedayati MT, Netea MG, Perlin DS, et al. COVID-19-Associated Candidiasis (CAC): An Underestimated Complication in the Absence of Immunological Predispositions? *J Fungi (Basel)*. 8 oct 2020;6(4).
9. Bishburg E, Okoh A, Nagarakanti SR, Lindner M, Migliore C, Patel P. Fungemia in COVID-19 ICU patients, a single medical center experience. *J Med Virol*. 27 oct 2020;
10. Cryptococemia in a patient with COVID-19: A case report - Khatib - 2021 - Clinical Case Reports - Wiley Online Library [Internet]. [cité 20 mars 2021]. Disponibles sur: <https://onlinelibrary.wiley.com/doi/10.1002/ccr3.3668>
11. Koehler P, Cornely OA, Böttiger BW, Dusse F, Eichenauer DA, Fuchs F, et al. COVID-19 associated pulmonary aspergillosis. *Mycoses*. 2020;63(6):528-34.