Main Article

Role of Inflammatory Markers as Prognostic Indicators in Treatment of Mucormycosis

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ABSTRACT

Introduction

Mucormycosis is opportunistic fungal infection characterized by extensive inflammation, necrosis and infarction of the involved tissues. It is associated with rise in levels of inflammatory markers [Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)]. This study was done to know the role of ESR, CRP as prognostic indicators in the treatment of covid-19 associated mucormycosis (CAM).

Materials and Methods

A retrospective descriptive study was conducted between May 2021 and December 2021 at atertiary centre. 315 patients with post-covid ROCM (Rhino-orbito-cerebral mucormycosis) were included in study. ESR and CRP were sent for all patients at the time of admission. Post operatively the same were repeated on post-op (POD) day 7, day 14, and day 30 during follow-up.

Results

243 (77.14%) patients were male and 72 (22.86%) were female. 6 patients with stage IV ROCM had recurrence of the disease in the post operative period. Mean ESR values in these patients at the time of admission, POD-7, 14, 30 were 98.17, 68.17, 44.00, 80.33 respectively. Mean CRP values in these patients at the time of admission, POD-7, 14, 30 were 58.50, 48.17, 26.33, 37.83 respectively.

Conclusion

Serial measurements of inflammatory markers (ESR, CRP) levels helps in the diagnosis and prognostication of ROCM along with clinical evaluation and imaging.

Keywords

Mucormycosis; Black Fungus; ESR; CRP

Mucormycosis is a rare, opportunistic fungal infection which causes angio-invasive disease leading to aggressive necrosis and infarction of the involved tissues.[1] A study in 2019 based on computational modelling revealed that the prevalence of mucormycosis in India before the covid-19 pandemic was 140 cases per million, translating to a mean of 171,504 cases in Indian population. The same study estimates a mean mortality rate of around 38 percent in well treated cases.[2]

During the second wave of the covid-19 pandemic in India, an increase in fungal infections, predominantly rhino-orbito-cerebralmucormycosis (ROCM), has been documented.[3] India has reported more than 47,000 cases of mucormycosis in three months (May to July 2021),

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and the actual figures are likely higher. The crisis of covid-19 associated mucormycosis was further worsened by an acute scarcity of amphotericin B caused by the large number of cases of mucormycosis.[4]

Underlying predisposing factors include uncontrolled diabetes mellitus, immunocompromised status, systemic use of corticosteroids, pre-existing respiratory pathology, cancer, and stem cell transplant.[5] The rhino-orbito-cerebral type is the most common form of the disease in India, followed by the pulmonary and cutaneous types.[6]

Because of the inflammation associated with mucormycosis, the levels of inflammatory markers [Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)] are likely to be increased whose levels can be measured in the blood. The radiological investigations will tell the extent of involvement and can be used as a guide to decide upon the extent of debridement. In the post-operative period, the dependability of these investigations in determining the response to treatment is limited because of the background inflammation. Hence, this study was conducted to examine serial measurements of ESR, CRP as a tool to evaluate response to the treatment.

Materials and Methods

A retrospective descriptive (record based) study was conducted between May 2021 and December 2021 at a tertiary centre. 315 patients with post covid RTPCR (Reverse transcriptase polymerase chain reaction) negative ROCM who were histopathologically and/or radiologically proven mucormycosis [European Organization for Research and Treatment of Cancer/ Mycoses Study Group (EORTC/MSG group) criteria][7] and who underwent surgery for post covid-19 mucormycosis were included in the study. RTPCR positive CAM patients who did not undergo any surgical procedures for CAM, patients with malignancy or tuberculosis were excluded from the study.

After obtaining approval from the institutional ethics committee, the patients fulfilling the inclusion criteria were enrolled for the study. Patient's demographic details, clinical features, laboratory test results, radiological reports and details of medical and surgical interventions performed were collected using a detailed proforma.

ESR and CRP were sent for all patients at the time of admission. Postoperatively the same were repeated on post-op (POD) day 7, day 14, and day 30 during follow-up. CRP value of 0-10mg/L was considered normal and >10mg/L as high. ESR value of 1-13mm/hr in males and 1-20mm/hr in females was considered as normal. The preoperative and postoperative ESR, CRP values were compared to determine their role as prognostic indicators in treatment of CAM.

Extent and severity of CAM was based on staging of ROCM by Honavar S Getal[8]- Stage 1 – Involvement of the nasal mucosa, Stage 2 –Involvement of the paranasal sinuses, perisinus inflammation, Stage 3 – Involvement of the orbit, Stage 4 – Involvement of the central nervous system. Data collected in the proforma was collated in MS Excel and analysed statistically using SPSS software version 24. Mean was calculated for ESR and CRP values in the preoperative and postoperative period and data was presented in tables and bar chart.

Results

315 patients were included in the study. 243 (77.14%) patients were male and 72 (22.86%) were female. Mean ESR and CRP values at the time of admission (Day 0), POD-7, 14, 30 in stage I, II, III, IV ROCM are mentioned in Fig.1 & 2.

Mean ESR values at day 0 , POD-7, POD-14, POD-30 are 51.784, 43.035, 31.686, 15.886. Mean CRP values at day 0 , POD-7, POD-14, POD-30 are 35.098, 29.072, 21.702, 8.006. The rise in levels of ESR and CRP were proportionate to the extent or severity of ROCM *[Pearson correlation is significant at 0.01 level (2-tailed)]*. Irrespective of the stage of the disease, there was decline in the levels of ESR, CRP in the postoperative period in response to the surgical debridement and systemic antifungals *[Pearson correlation is significant at 0.01 level (2-tailed)]*.

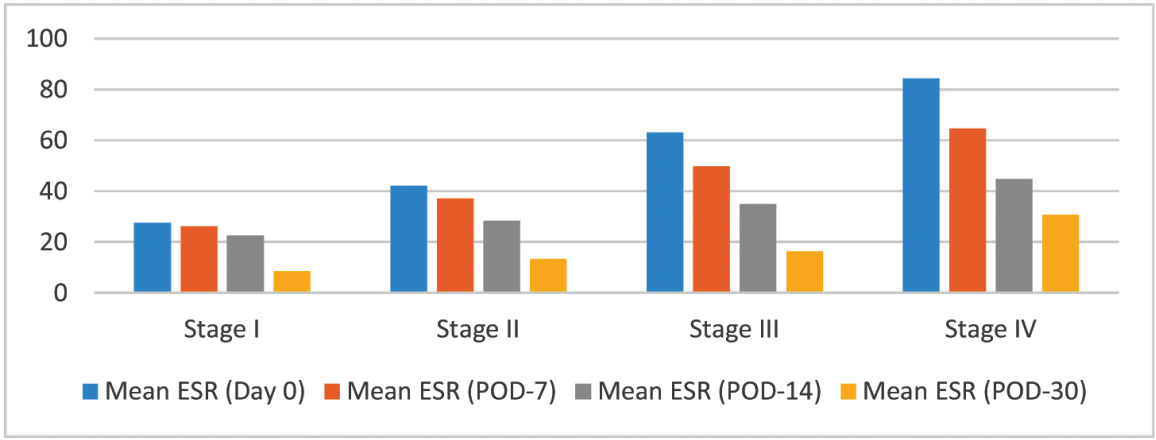

Fig. 1. Mean ESR values at Day 0, POD-7, 14, 30 & stage of ROCM

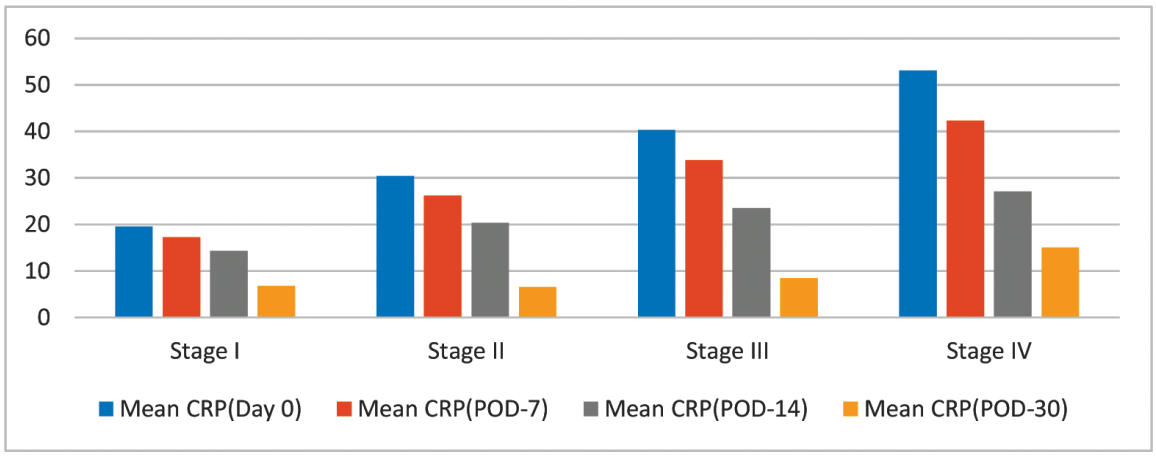

Fig. 2. Mean CRP values at Day 0, POD-7, 14, 30 & stage of ROCM

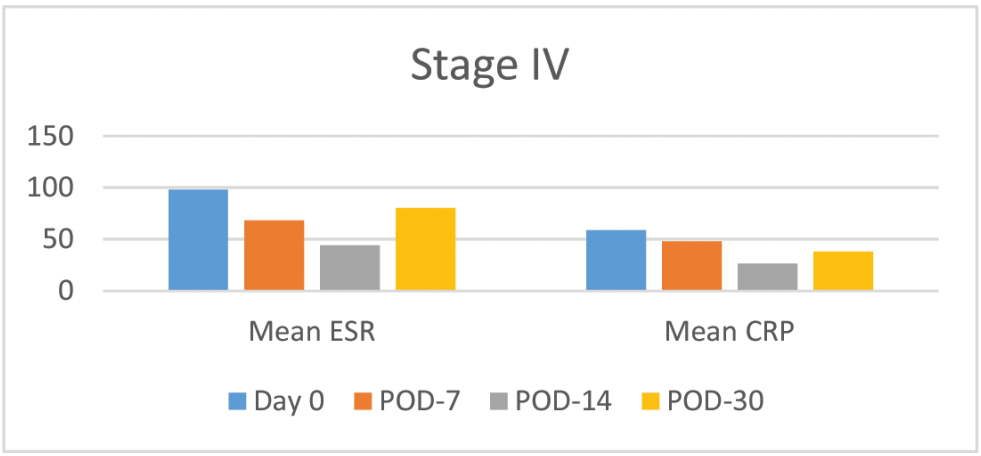

Fig. 3. Mean ESR & CRP values in Stage IV ROCM patients with recurrence

6 patients with stage IV ROCM had recurrence of the disease in the postoperative period. Mean ESR values in these patients at the time of admission, POD-7, 14, 30 were 98.17, 68.17, 44.00, 80.33 respectively. Mean CRP values in these patients at the time of admission, POD-7, 14, 30 were 58.50, 48.17, 26.33, 37.83 respectively (Fig. 3). There was increase in levels of inflammatory markers at POD-30 *[Kendall's tau-b correlation is significant at 0.01 level (2-tailed)]* which correlated with occurrence of symptoms of recurrence and imaging findings.

Discussion

The erythrocyte sedimentation rate (ESR) is a common hematology test that may indicate and monitor an increase in inflammatory activity within the body caused by one or more conditions such as autoimmune disease, infections or tumors. It is elevated in anemia, arteritis, infections (including bone and joint), kidney disease, low serum albumen, lupus, lymphoma, multiple myeloma, polymyalgia rheumatica, red blood cell abnormalities, rheumatoid arthritis, systemic vasculitis, Thyroid disease, Waldenstrom macroglobulinemia. High ESR values > 100mm/hr is seen in malignancy, tuberculosis, multiple myeloma, temporal arteritis etc. ESR is not specific for any one disease but is used in combination with other tests to determine the presence of increased inflammatory activity. The ESR has long been used due to its reproducibility and low cost.[9]

The ESR test measures the rate at which the red blood cells (RBCs), or erythrocytes, in a sample of whole blood, fall to the bottom of the Westergren tube. This process of "falling" is called sedimentation. RBCs typically fall at a faster rate in people with inflammatory conditions. These conditions lead to an increase in the number of proteins in the blood. This increase causes red blood cells to stick together (clump) and settle at a faster rate. A group of RBCs that are clumped together will form a stack (similar to a stack of coins) called a rouleaux (pleural is rouleaux). Rouleaux formation is possible because of the particular discoid shape of RBCs.[10]

Serum CRP is frequently used as a biomarker of infection. CRP was first discovered in 1930.[11] Human CRP is composed of multiple subunits of polypeptide, and it is an acute-phase protein produced by the liver in response to inflammatory cytokines. Currently the most widely used biomarker of systemic infection is CRP.[12]

A study was conducted by I Kostiala to find out the CRP response induced by fungal infections, serial determinations of CRP were performed by single radial immunodiffusion in four groups of patients with fungal disease in order to determine its use as an aid to diagnosis. They have concluded that deep-seated fungal disease has ability to induce high CRP values similar to our study.[13]

A study conducted by Marková Metal in 2013 concluded that the combination of substantially elevated CRP concentrations and persisting low procalcitonin levels, may indicate invasive fungal infection and thereby lead to early initiation of specific therapy in both neutropenic and non-neutropenic patients.[14]

According to the study conducted by Cho HJ etal, it was concluded that elevation of CRP, in particular, was an independent predictor of poor outcomes and should be monitored appropriately.[15]

The above studies prompted us to use serial ESR, CRP measurements as a guide to manage our patients. The second wave of covid-19 in India saw an unusual and steep rise in mucormycosis in both active and recovered from covid infection. Dysregulated immune response in COVID-19 characterized by exuberant activation of innate immune system, elevation in systemic inflammatory markers (C-reactive protein (CRP), ferritin, lactate dehydrogenase (LDH) and D-dimer), aberrant pro-inflammatory cytokine secretion (Interleukin – 6 (IL-6), soluble IL-2 receptor [IL-2R], IL-10, TNF-á) by alveolar macrophages and depleted adaptive immune response (decline in CD4+ T cell, CD8+ T cell, Natural killer cell and decreased Interferon Gamma (IFN-ã) expression in CD4+ T cells), endothelial dysfunction were seen in individuals with CAM.[16]

In our study, we studied the correlation between the mean ESR and CRP values with the extent of severity of ROCM. We observed the mean values of ESR, CRP at the time of admission were high in stage III and IV disease

Fig. 4. Case of Stage III ROCM with cutaneous involvement

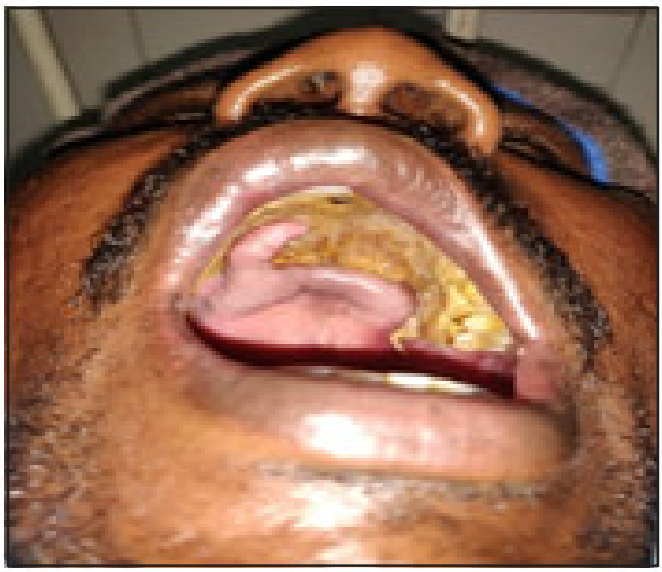

Fig. 5. Case of Stage III ROCM with palatal involvement

which showed the extensive involvement (clinically & radiologically) and inflammation as compared to stage I and II ROCM (Fig. 4 & 5). The values were in proportion with stage of ROCM.

Management of ROCM at our centre included early surgical debridement of the necrotic tissues till fresh bleeding (healthy mucosa) is encountered, along with intravenous antifungals therapy (IV Liposomal amphotericin B, Posoconazole based on the availability for 2 weeks followed oral posoconazole for 4-6 weeks). Postoperatively, patients were followed up with weekly diagnostic nasal endoscopy (DNE) and cleaning, ESR, CRP at POD-7, 14, 30 and for emergence of new symptoms indicating recurrence.

There was not much of decline in mean ESR and CRP values at POD-7 compared to preoperative period which might be due to the postoperative inflammation and response of the body to the surgical debridement. We observed that there was gradual decline in mean ESR and CRP values in proportion to the recovery in the postoperative period and values were almost normal at POD-30 especially in stage I, II, III ROCM as majority of these patients were symptom free.

6 (1.9%) patients in stage IV ROCM presented with recurrence after 1 month of surgery. There was a rise in ESR and CRP values at POD-30 in these patients. Serial measurements of ESR and CRP in patients with ROCM appears to be a dependable investigation as they help in monitoring the recovery and recurrence along with clinical symptoms, diagnostic nasal endoscopy and radiological investigations.

Mucormycosis is associated with very high levels of inflammatory markers based on the severity of the infection, due to the response of immune system to the fungal pathogen. Measurement of ESR, CRP is an easy and readily available tool along with clinical evaluation and imaging in evaluating the extent of disease. It helps in the perioperative and postoperative monitoring of response to treatment (near normal values were achieved when there was complete clearance of the disease). ESR & CRP values helped in identifying the recurrence during the early postoperative period where radiological findings cannot give valuable information due to background inflammation.

Conclusion

Mucormycosis is acute invasive fungal infection which causes extensive inflammation and necrosis of the involved

sites. Serial estimation of ESR and CRP levels assists in the diagnosis and prognostication of ROCM along with clinical evaluation and imaging in the early stages of disease and in detecting early recurrence after the surgical intervention.

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