

Case report,

Hemophagocytic Lymphohistiocytosis Syndrome as Presenting Sign for Acute Monocytic Leukaemia- A Case Report.

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Abstract:

Background: Hemophagocytic lymphohistiocytosis (HLH) is a rare aggressive syndrome of excessive immune activation. Clinical manifestations of this syndrome mimic various other clinical conditions making the diagnosis harder to achieve. These manifestations are believed to be a result of cytokine storm which leads, eventually, to a multi-organ failure and eventually death. The latter two might be prevented if HLH was diagnosed early. HLH is classified into primary consist of monogenic disorders and secondary occurs as a complication in various settings such as infection, autoimmune disease, and malignancy.

In hematologic malignancies, HLH is classically associated with specific entities, mainly, lymphoma or induced by treatment-related infections. Acute myeloid leukemia, on the other hand, is less common trigger with only few case reports.

Case presentation: An 83-years-old, 5 years free of transitional cell man, presented with unstable atrial fibrillation was intubated and shortly after that he developed a multi-organ failure. Bicytopenia and a high level of ferritin aroused a clinical suspicion of HLH syndrome. Further evaluation revealed high levels of soluble interleukin 2 receptors and no activity of natural killer's cells. A bone marrow was performed and it did not show phagocytosis, however, acute myeloid leukemia (AML) was diagnosed. AML was suggested to be associated with chemotherapy that our patient received 5 years earlier.

Conclusion: Hemophagocytic lymphohistiocytosis can be present as a multi-organ failure requiring a high index of suspicion. Chemotherapy related-AML can be a trigger for HLH.

Key words: hemophagocytic lymphohistiocytosis, acute myeloid leukemia, chemotherapy-associated with acute myeloid leukemia, multi-organ failure.

Background:

Hemophagocytic lymphohistiocytosis (HLH) is a rare aggressive and fatal syndrome of excessive immune activation. HLH is reported in all ages, but it is more common in children.¹ it can mimic various medical conditions making the diagnosis even harder, multi-organ failure, and potential death is the result of delayed diagnosis. In this syndrome, the cytotoxic activity of CTL and natural killer's cells are impaired, failing to eliminate stressed cells from the body, and, instead, continuously secreting inflammatory

cytokines. Macrophages are activated by these cytokines and themselves produce cytokines. This results in a vicious cycle that amplifies the cytokine secretion generating a cytokine storm and multi-organ failure.²⁻⁵

Hemophagocytic lymphohistiocytosis is classified into two subgroups – Primary HLH and Secondary HLH.

While primary HLH consists of monogenic disorders that mainly affect the perforin mediated cytotoxicity of cytotoxic T lymphocytes and

natural killer cells.⁶⁻⁷ The secondary HLH occurs as a complication in various settings such as infection mainly EBV, autoimmune disease, and malignancy. In hematologic malignancies, HLH is classically associated with specific entities. T cell lymphoma or NK/T cell lymphoma and intravascular large B cell lymphoma, or induced by treatment-related bacterial, viral or fungal infections.⁸⁻¹⁰ In patients with acute myeloid (AML), HLH has been occasionally described in case-reports. AML patients may be prone to develop HLH due to their disease and/or treatment-related impaired immune response, and their high susceptibility to severe infections, which act as triggering factors.¹¹ Diagnosing and treating the underlying conditions in secondary HLH is of a great value since it can lead to clinical improvement of the HLH allowing the patient to avoid more toxic therapy (like, hematopoietic cell transplant).¹²⁻¹³ HLH is diagnosed based on the HLH-2004 diagnostic criteria (Table 1). To diagnose HLH, five or more of eight criteria must be fulfilled unless there is a family history or molecular diagnosis consistent with HLH. The eight criteria are: Fever, Splenomegaly, Peripheral blood cytopenia, Hypertriglyceridemia, Hemophagocytosis in bone marrow, spleen, lymph node or liver, Low or absent NK cell activity, Ferritin >500 ng/ml, Elevated soluble interleukin-2-receptor (sIL2-R). It is worth to note that a diagnosis in certain circumstances could be established with less than 5 criteria. Moreover, treatment should not be delayed even if less than five criteria were present. Less common clinical features that are not included in the diagnostic criteria include liver dysfunction and coagulation abnormalities, neurological findings, respiratory system involvement such as ARDS like syndrome which might necessitate ventilator support, kidney involvement, and bleeding.¹⁵⁻¹⁷ In this paper, we present a rare case report of an 83-years-old man (the oldest as far as we know), who was presented with multi-organ involvement and eventually was diagnosed with HLH associated with chemotherapy-related AML.

Case presentation:

An 83-years-old man whose medical history included: 5 years free of TCC that was treated with chemotherapy, in addition to ischemic heart disease, congestive heart failure, chronic atrial fibrillation, and other cardiovascular risk factors, was presented in the emergency department with shortness of breath. His initial vital signs and

physical examination were normal. Further evaluation at that point included: ECG showing atrial fibrillation around 100 bpm, chest x-rays showing cardiomegaly with no evidence of pulmonary edema, and blood tests revealing: new onset of mild anemia and mild thrombocytopenia, elevated INR, mildly elevated bilirubin, acute prerenal kidney injury and metabolic acidosis (Figure 1). Accordingly, the patient was admitted to an internal medicine department. Upon his presentation to the internal department he becomes hemodynamically unstable: atrial fibrillation around 130 and hypotension (60/40), necessitating an electrical cardioversion that was not effective and instead amiodarone was started. The next day he continued to be unstable and subsequently was intubated and was transferred to the ICU.

In the ICU, the patient was re-evaluated: he was tachycardic and hypotensive, vasopressors were started. Blood tests were taken this time showing mainly worsening of the cytopenia and worsening of kidney function requiring a hemodialysis. Interestingly, extreme hyperferritinemia was documented as well (figure 1). Blood, urine, and sputum cultures were obtained, and broad-spectrum antibiotics were started immediately, blood products were given too. Chest x rays and abdomen US were performed showing no evidence of infection. The next day a gastroscopy and total body CT were performed but no source of bleeding was seen. High level of ferritin accompanied with multi-organ involvement including most importantly hematological since bi-cytopenia was developed, but also cardiovascular, respiratory, and nephrological involvement, made HLH syndrome a reasonable diagnosis. For the establishing the diagnosis five out of eight criteria needed to be fulfilled: cytopenia and high levels of ferritin were already present, NK activity test was performed and showed 0% activity and soluble IL-2 receptor levels were taken and was shown to be high. (Figure 1). Other criteria like fever, splenomegaly, hypertriglyceridemia, hyperfibrinogenemia did not exist. A bone marrow biopsy was arranged but meanwhile, IV steroids for suspected HLH were administered. Since secondary HLH was more reasonable (based on our patient's age), more Blood, urine, and sputum cultures were obtained, PCR for both EBV and CMV was taken and shown to be negative. Blood smear and peripheral FACS showed an excessive monocytosis with less than 1% of blasts which made myelodysplastic syndrome, rather than leukemia, a reasonable

diagnosis at this point, but a second Blood smear and peripheral FACS was performed and showed more than 30% of blasts. Finally Bone marrow biopsy results came back excluding phagocytosis but on the other hand confirming the diagnosis of acute myeloid leukemia.

Discussion and conclusion:

Hemophagocytic lymphohistiocytosis (HLH) is a hyperinflammatory syndrome characterized by significant CD8 T-cell and macrophage activation and severe hypercytokinemia. This hypercytokinemia can lead to severe multi-organ dysfunction, which often requires aggressive supportive care within the intensive care unit as in our case. Thus, a high index needs to be present in these patients and appropriate work up needs to be performed. A major issue in establishing the diagnosis of HLH derives from the fact that many patients do not meet the required five diagnosis criteria. Still, it is convenient to diagnose and treat patients as HLH even with less than five criteria. In our case, only four of the criteria existed but we believe they were sufficient for several reasons: first, the presence of a cytokine storm induced multi-organ failure with no other overt etiology, especially infection. Second, Hyperferritinemia in the absence of other condition that is known to cause high ferritins such as liver disease, chronic transfusions, or overt infection. Lastly, a positive immunological studies profile NK activity and soluble interleukin 2 receptors levels. Natural

killers could be impaired in hereditary conditions and infections but both were irrelevant in our case. Soluble interleukin 2 receptors levels are considered to be a marker of the disease. In our case, an 83-years-old man, secondary HLH was more reasonable, therefore, a search for an underlying trigger was conducted, infection workup excluded this option. A total body CT was performed excluding a malignancy mainly a lymphoma which is considered to be a leading cause in secondary HLH. A biopsy later showed no phagocytosis but did reveal acute myeloid leukemia - which we believe was related to chemotherapy he received five years ago. An autoimmune disease seemed less rational in our case, but an appropriate workup advisable in relevant cases. Hemophagocytic lymphohistiocytosis syndrome secondary to acute myeloid leukemia is a rare entity with a limited number of case reports. It is usually associated with diagnosed active AML and treatment-related. What made our case more interesting was the fact that no previous diagnosis of AML was made for our patient, instead the diagnose was made during hospitalization.

To conclude: Hemophagocytic lymphohistiocytosis can be present as a multi-organ failure requiring a high index of suspicion. Chemotherapy related AML can be a trigger for HLH.

HLH DIAGNOSTIC CRITERIA

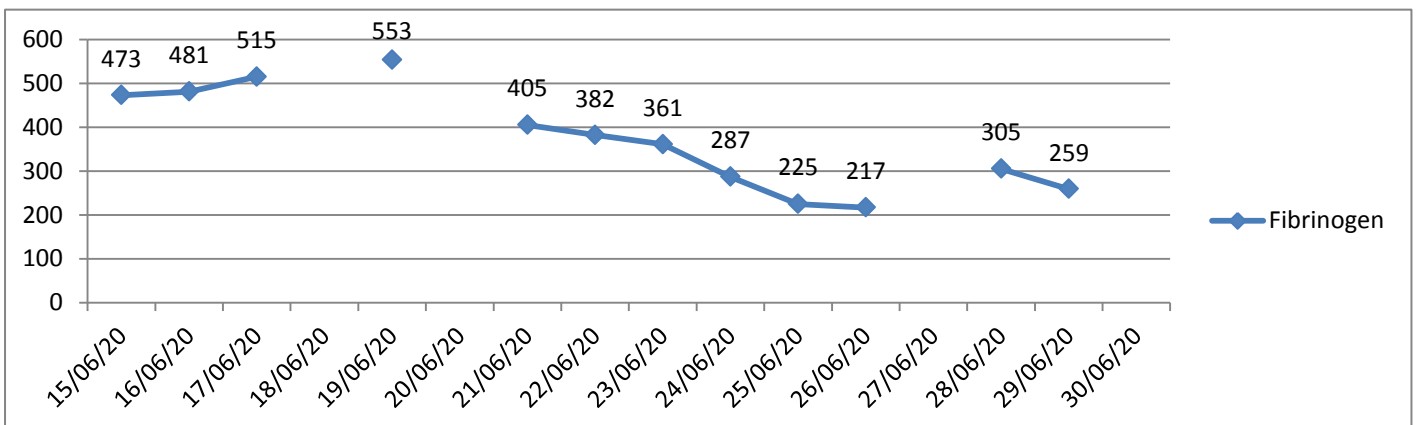
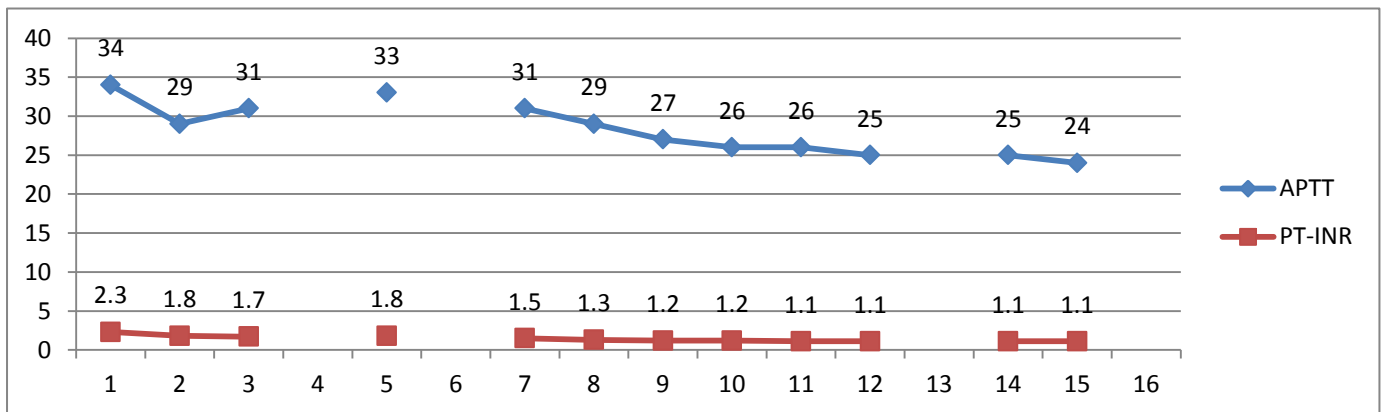
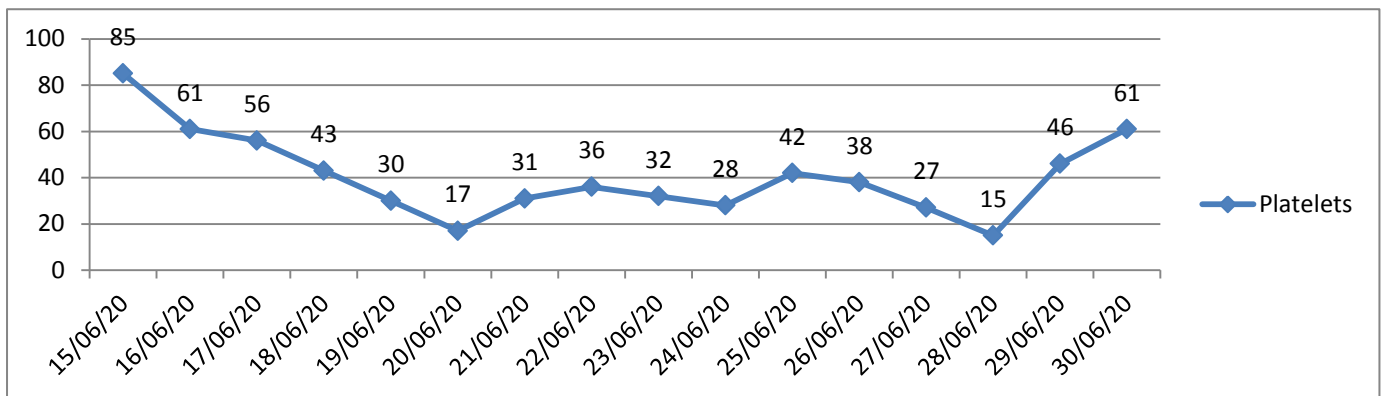
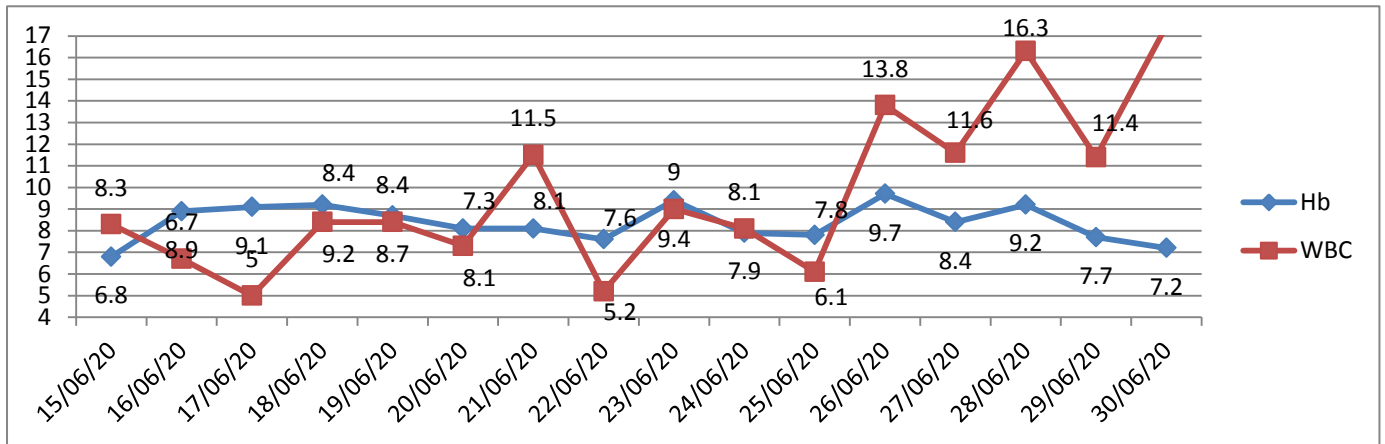
At least 5 out of 8 criterias

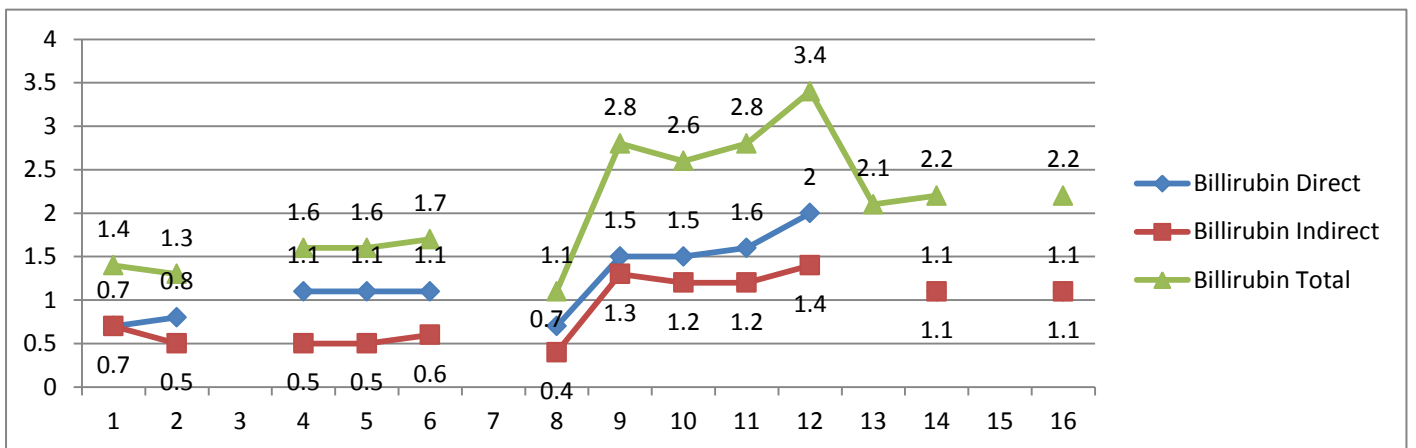
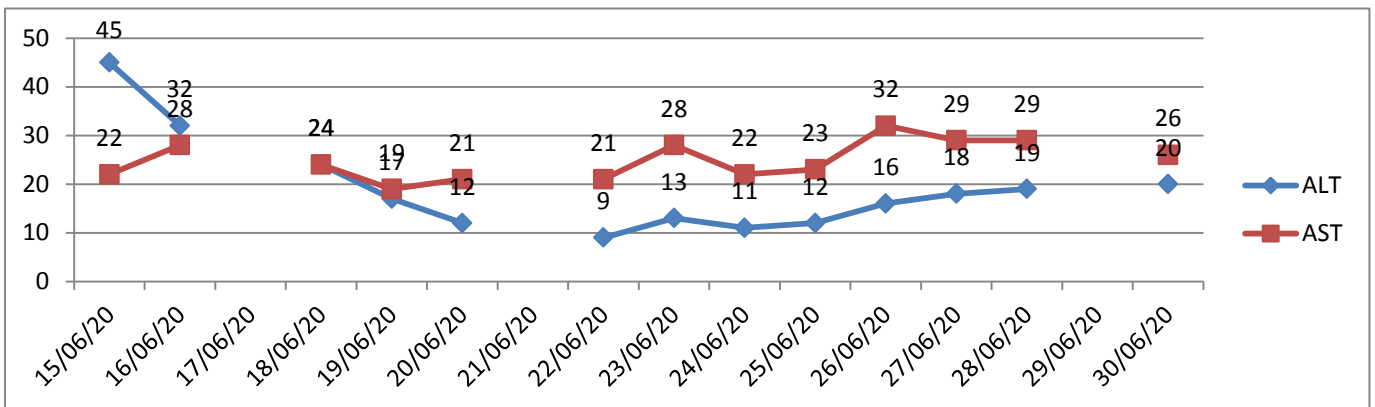
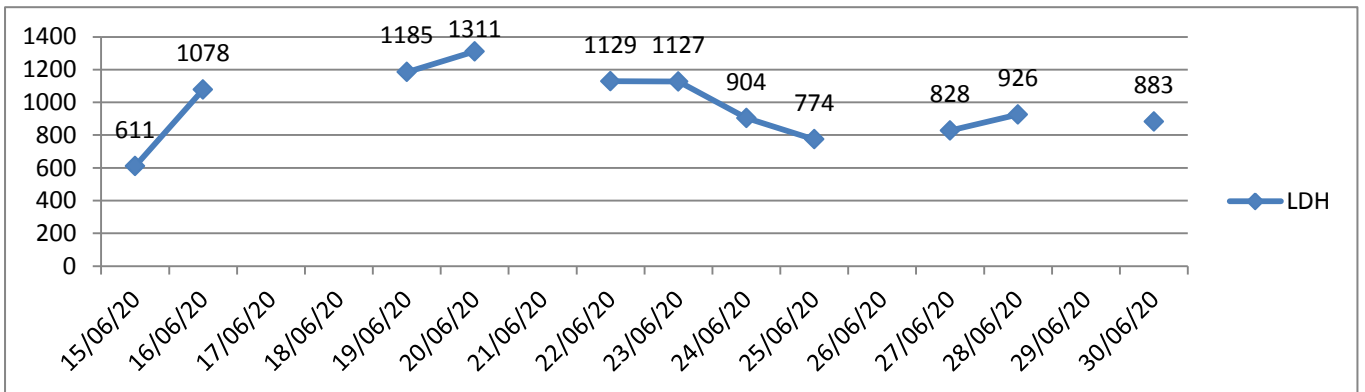
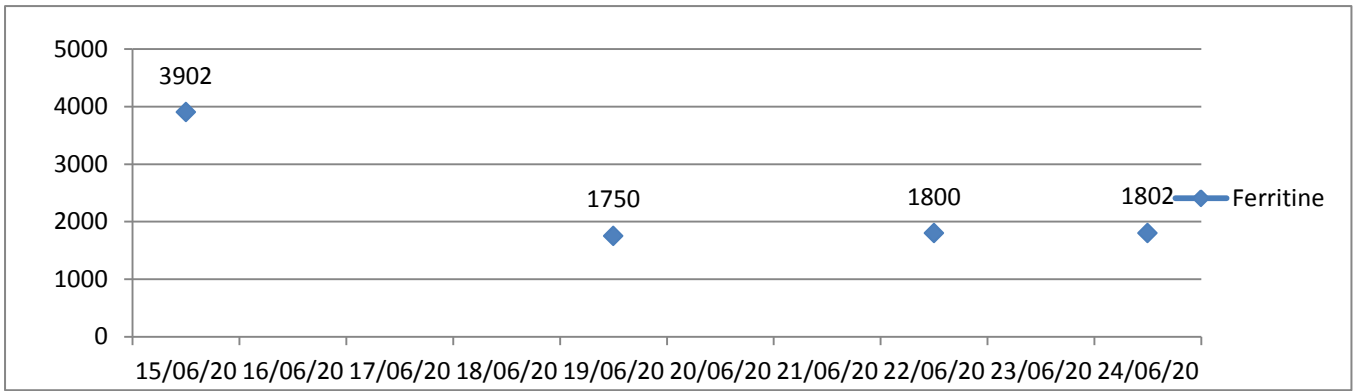
1	Fever ≥38.5°C
2	Splenomegaly
3	Peripheral blood cytopenia, with at least two of the following: hemoglobin <9 g/dL (for infants <4 weeks, hemoglobin <10 g/dL); platelets <100,000/microL; absolute neutrophil count <1000/microL
4	Hypertriglyceridemia (fasting triglycerides >265 mg/dL) and/or hypofibrinogenemia (fibrinogen <150 mg/dL)
5	Hemophagocytosis in bone marrow, spleen, lymph node, or liver
6	Low or absent NK cell activity
7	Ferritin >500 ng/mL (the author prefers to consider a ferritin >3000 ng/mL as more indicative of HLH)
8	Elevated soluble CD25 (soluble IL-2 receptor alpha [sIL-2R]) two standard deviations above age-adjusted laboratory-specific norms

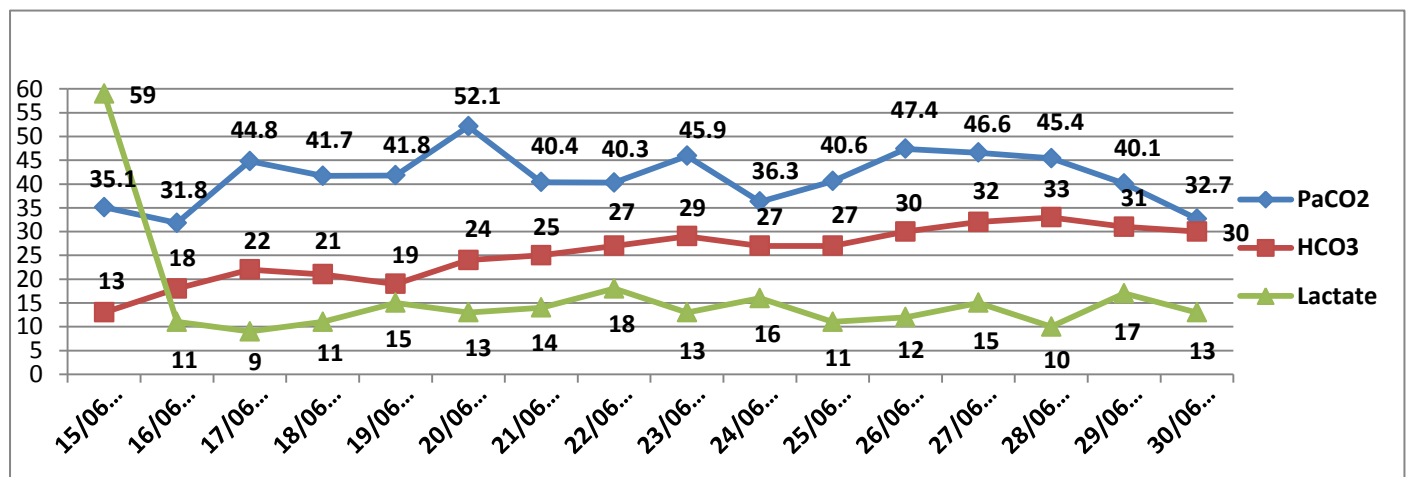
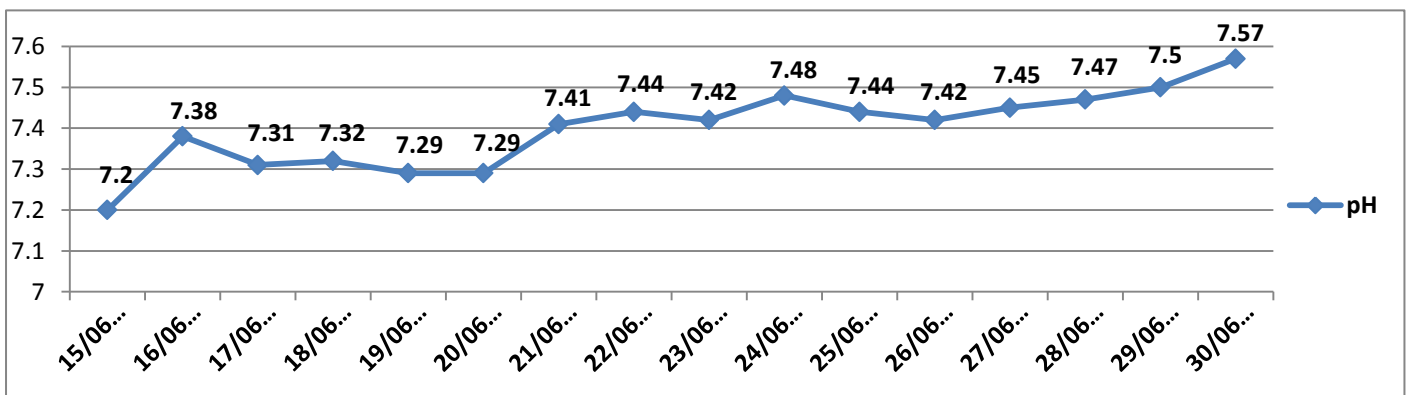
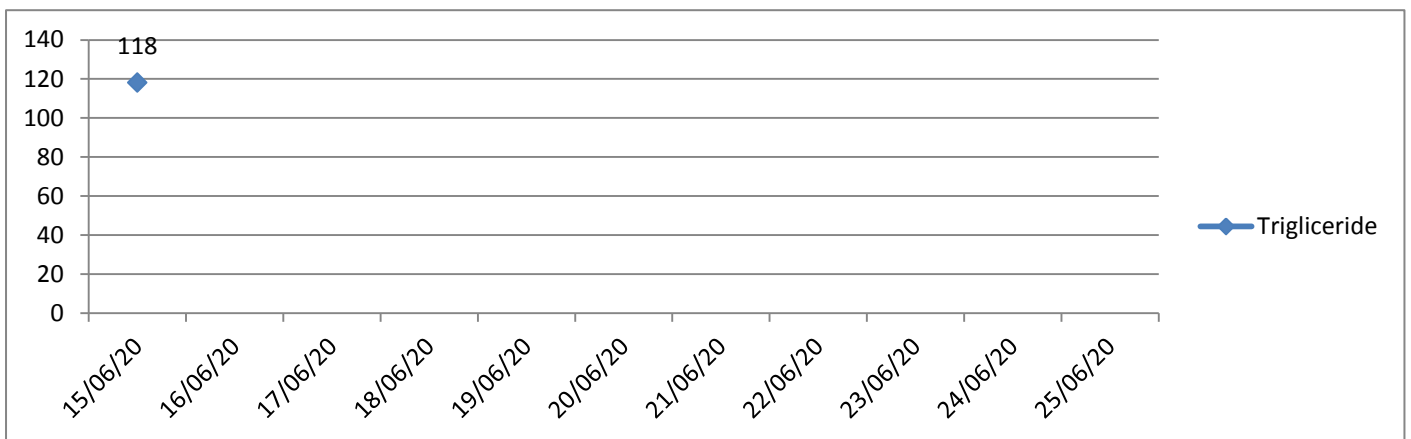
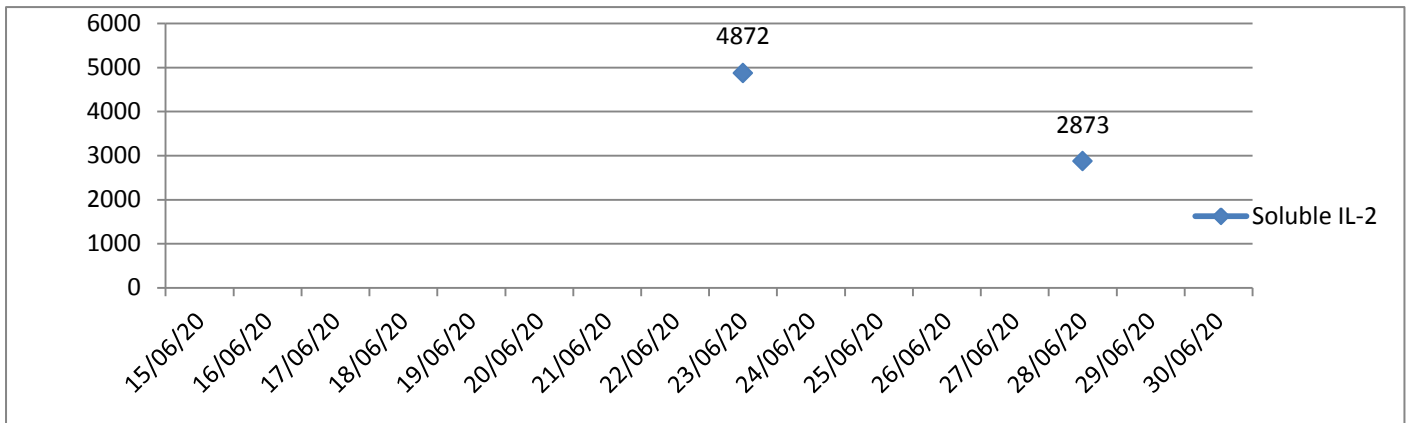
OR

1	A patient with CNS symptoms, cytopenias, fever, and ferritin over 3000 ng/mL or rapidly rising ferritin or elevated sCD25
2	A patient with CNS symptoms, hepatitis, coagulopathy, and ferritin over 3000 ng/mL or rapidly rising ferritin or elevated sCD25
3	A patient with hypotension, fever, no response to broad spectrum antibiotics, and ferritin over 3000 ng/mL or rapidly rising ferritin or elevated sCD25

Figure 1: laboratory tests during hospitalization







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