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Case Report

Progressive Thrombocytopenia and Clinical Deterioration with Initial Diagnosis of Esophageal Cancer-Secondary Hemophagocytic Lymphohistiocytosis as a Complicating Cause

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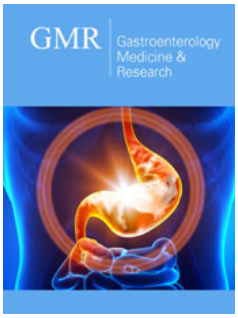

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Case Report

A 52-year-old male patient presented in the emergency department with fatigue and persistent back and flank pain. Computed tomography revealed lymphadenopathy and disseminated osseous lesions. Staging was completed and a low differentiated signet ring cell carcinoma of the distal esophagus (AEG I), UICC stage IV [1], was diagnosed. Immunohistochemistry showed expression of human epidermal growth factor receptor 2 (HER2)/neu and E-cadherin without expression of programmed death-ligand [1]. No microsatellite instability was detected. Palliative polychemotherapy with 5-fluorouracil, folinic acid, oxaliplatin and docetaxel (FLOT) was initiated. Due to progressive pancytopenia with transfusion-dependent thrombocytopenia, abnormal renal function tests, fever and rapid clinical deterioration, we suspected malignancy-associated Thrombotic Microangiopathy (TMA), and therefore promptly initiated daily plasmapheresis. However, no objective response upon plasmapheresis was observed, while extended laboratory tests revealed elevated levels of lactate dehydrogenase (1477U/l, range: 135-250U/l), ferritin (4410µg/l, range 30-400µg/l), triglycerides (366mg/dl, range >200mg/dl) and soluble interleukin 1 receptor (1807IU/ml, range: <710IU/ml). Abdominal ultrasonography revealed splenomegaly. Notably, bone marrow biopsy revealed extensive carcinomatosis and activation of stromal macrophages (Figure 1). According to those findings and a calculated H-score (*reference: http://saintantoine.aphp.fr/score/*), malignancy associated Secondary Hemophagocytic Lymphohistiocytosis (sHLH) was diagnosed. Thus, we initiated treatment with interleukin (IL)-1 inhibition (Anakinra), prednisolone and continuation of polychemotherapy, resulting in a significant clinical improvement and decline of ferritin (1990.4µg/l) and lactate dehydrogenase (860U/l) levels. Subsequently, the patient successfully completed six cycles of polychemotherapy but eventually died due to progressive esophageal carcinoma. What do we learn from this unusual case? First, distinguishing sHLH from TMA in the context of rapid onset thrombocytopenia along with clinical and laboratory deterioration is extremely challenging. However, extensively elevated ferritin levels are indicative for HLH and may guide diagnostic considerations early on [2]. Second, Bone Marrow Carcinomatosis (BMC) due to gastric or esophageal carcinoma is a highly rare event [3,4], and concomitant sHLH is a yet underreported, but potentially life-threatening phenomenon in this context. HLH is a hyperinflammatory syndrome leading to an uncontrolled cytokine storm with an all-cause mortality of approximately 40% in adults [5]. Although exact path mechanisms remain unclear, dysregulation of immune homeostasis due to chemotherapy and underlying malignancy might lower the threshold for triggering sHLH [6]. However, in this patient we considered BMC as driver of sHLH and therefore decided to continue chemotherapy. Third, therapeutic decision-making remains challenging due to a lack of validated treatment protocols in adults

with sHLH. In a recent report from China, two gastric cancer patients with sHLH were treated with glucocorticoids plus etoposide and etoposide/doxorubicin, respectively, but after clinical recovery sHLH relapsed [7]. As IL-1 is crucial in the pathogenesis of HLH, we opted for subcutaneous application of anakinra-no adverse events occured and our patient quickly recovered from sHLH.

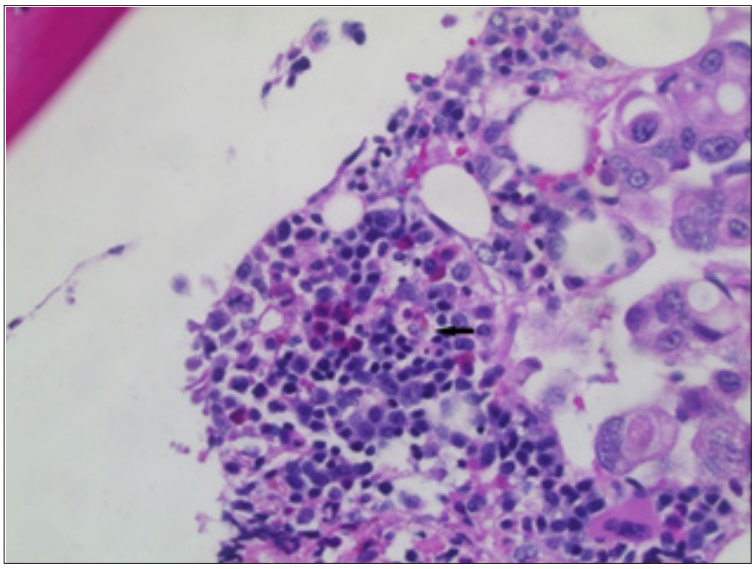

Figure 1: Carcinomatosis of the bone marrow with remaining haematopoiesis and activation of stromal macrophages. Shown is a representative hematoxylin and eosin staining of the bone marrow biopsy (40x magnification). An activated stromal macrophage is indicated by the arrow.

Conclusion

In conclusion, considering sHLH in patients with solid tumors and identifying BMC as a potential trigger, remains challenging in the clinical routine. Once the diagnosis is established, anakinra is an effective and well tolerated first line treatment option with a favorable benefit-risk profile.

Conflict of Interest

All authors declare that they have no conflict of interest.

Ethical Approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent

Informed consent was not obtained from the patient referenced in the case report (deceased). Multiple attempts were made to reach his next of kin to obtain consent, but we were unable to make contact with his family.

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