Because of insufficient disease control, treatment with a TNF-inhibitor (infliximab) was started with apparent improvement of intestinal symptoms. However, persistent granulomatous inflammatory disease of the distal portion of the ileus-rectal anastomosis persisted. Moreover, the patient presented recurrent HLH episodes that required high dose of glucocorticoid and cyclosporine-A treatment. Except one HLH episode related to a varicella zoster infection, the other HLH events were most likely triggered by his underlying inflammatory condition. During the HLH episodes levels of IL-1β were moderately elevated (10.860 pg/ml) the IFN-γamma-induced chemokine CXCL9 was markedly high (21.871 pg/ml) and remained markedly elevated also during clinical and laboratory HLH remission (3.121 pg/ml and 9.929 pg/ml respectively). Considering the early disease onset, primary immunodeficiency and early intestinal bowel disease onset were genetically ruled out as well as chronic granulomatous diseases through extensive NGS panels. WES revealed carriage of a private (MAF: 1/12568, TOPMED), predicted pathogenic (CADD: 31), homozygous variant of WNT6 (c.793G>C; p.(Asp265His); NM_006522.3). The patient is now partially controlled on low dose of oral glucocorticoid (0.1 mg/kg), cyclosporine-A (8mg/kg) and antimicrobial treatment.

Conclusion: WNT signaling has been primarily described as a regulatory pathway in ontogeny and homeostatic processes. Schaale et al. demonstrated that WNT6 is expressed in granulomatous lesions in the lung of Mycobacterium tuberculosis–infected mice. Moreover, they found that the transcription factor c-Myc is significantly induced in murine macrophages by WNT6. This identifies WNT6 as a novel factor driving macrophage polarization toward an M2-like phenotype, suggesting a role for WNT6 in macrophage differentiation. Our case suggests defective function of WNT6 might be involved in the development of a granulomatous disease. WNT6 role in macrophage differentiation and polarization might also be important in the activation of the IFN-gamma pathway and in recurrent HLH episodes.

REFERENCES:

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Background: Despite continuous advances in the identification of novel causative genes, several patients with a clinical autoinflammatory phenotype remain unclassifiable.