Mass cytometry in POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, skin changes) syndrome: looking for a needle in a haystack

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In their current paper, Kourelis *et al.* profile the different immune cells within the bone marrow (BM) of patients with POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M-protein, skin changes) (Kourelis *et al.*, 2019). POEMS syndrome is a paraneoplastic entity, due to an excessive inflammatory reaction that is related to a monoclonal plasma cell population (Keddie & Lunn, 2018). Elevations of pro-inflammatory cytokines, such as interleukin 1β, interleukin 6, and tumour necrosis factor α, have all been found, while elevated vascular endothelial growth factor levels contribute by endothelial cell activation and increasing vascular permeability (Dispenzieri & Buadi, 2013). The malignant component of this disorder is only small, while most of the symptoms (polyneuropathy, skin changes and lymph node disorders) are caused by the chronic inflammation.

Further deciphering this inflammatory reaction urged Kourelis *et al.* to perform mass cytometry on BM samples from patients with POEMS syndrome and compare these profiles with patients with monoclonal gammopathy of undetermined significance (MGUS) because these patients also present a monoclonal gammopathy, but without the systemic complications seen in POEMS syndrome.

The authors introduced mass cytometry to profile the different immune cells. In the past, this profiling was commonly done by flow cytometry. Instead of fluorochrome-labelled antibodies, mass cytometry uses heavy metal isotopes to label antibodies, and the labelled cells are analysed by high-throughput spectrometry (Galli *et al.*, 2019). In this way, mass cytometry or cytometry by time-of-flight (Cytof) fuses the principles of mass spectrometry and flow cytometry. Up to 50 parameters can be studies per cell. Because staining and acquisition is simultaneously realised, the risk of technical sample variations between samples is reduced. This makes Cytof suitable for automated analysis of large sample groups, in which even rare immune subsets can be identified. Cytof was previously used in other plasma cell disorders to illustrate the immune modulatory action of daratumumab in multiple myeloma (Adams *et al.*, 2019), to profile immune cell populations in myeloma and precursor cell entities at diagnosis (Kourelis *et al.*, 2019; Marsh-Wakefield *et al.*, 2019; Bailur *et al.*, 2019) and in case of resistant disease to daratumumab or immunomodulatory agents (Neri *et al.*, 2018).

Although the number of patients that were included in this study was low, the authors identified in their current work different subsets within CD4 and CD8 cells. More interestingly, increases in double-positive T cells and programmed cell death protein 1 (PD-1)-positive CD4 T cells were seen in the BM of patients with POEMS (Kourelis *et al.*, 2019). The overexpression of PD-1 was not confirmed by immunohistochemistry on BM sections.

The potential implication of the PD-1/programmed death receptor-ligand 1 (PDL-1) axis in the pathophysiology reminds us on the therapeutic efficacy of nivolumab in Hodgkin lymphoma (Ansell *et al.*, 2015). This lymphoma entity is also characterised by sparse malignant cells (Hodgkin and Reed–Sternberg [HRS] cells) that constitute <5% of the tumour bulk, but HRS cells grow and survive with the help of interactions with and within a heterogeneous background of inflammatory cells. Different immune checkpoint regulators are expressed by HRS cells, but PD-L1 is found to be universally present on HRS cells due to a genetic amplification at chromosome 9 (De Goycoechea *et al.*, 2019). This overexpression explains the therapeutic efficacy of immune checkpoint inhibition in this malignancy.

The current work of Kourelis *et al.* illustrates well the capacities of mass cytometry: it gives insights into the pathophysiology of diseases and allows the discovery of novel targets or biomarkers. Profiling of immune subsets is currently its main application, but the fast development of this technique will allow a broadening to other fields.

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