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Chronic inflammatory demyelinating polyneuropathy as a paraneoplastic manifestation of colorectal carcinoma: What do we know?

The pathogenesis of chronic inflammatory demyelinating polyneuropathy (CIDP) remains highly debated among experts. In recent times, literature has divulged a riveting yet plausible association between colorectal carcinoma and CIDP as its paraneoplastic ramification. Initially, research suggested that chronic inflammatory demyelinating polyneuropathy (CIDP) was caused solely by macrophages [1]. However, recent studies have insinuated towards an alternative pathogenesis, one involving autoantibodies against paranodal junction proteins [2]. These two distinct mechanisms are the primary contenders responsible for the development of CIDP, rendering it an elusive paraneoplastic manifestation of colorectal carcinoma.

Traditionally, macrophages have been purported to be responsible for the phagocytosis of the myelin surrounding peripheral neurons [1]. A recent study divulged that macrophage-induced demyelination is not only responsible for classical CIDP but also atypical CIDP such as distal acquired disseminated symmetric (DADS) CIDP, multifocal acquired demyelinating sensory and motor (MADSAM) CIDP, and pure sensory subtypes [3]. However, of note, this was not found to be true in all cases [3]. A teased-fibre preparation of a sural nerve biopsy taken from the same patients showed sections without myelin due to macrophages-induced phagocytosis [2]. Moreover, electron microscopy showed that the macrophages were found within the tubes of basement membrane, which itself is normally encompassed by myelin [2]. Yet myelin debris was detected in macrophage cytoplasm [2]. On the other hand, the cytoplasm of the Schwann cells, found in the outermost layer of the myelinated fibers, were intact and unaffected by macrophages [2].

Factors responsible for the phagocytosis of myelin are still unclear [2]. A recent study examining a sural nerve biopsy through an electron microscope showed that macrophages tend to target specific sites of the myelinated fibers [4]. In particular, the region surrounding the nodes of Ranvier and the internodes in certain patients appear to be major sites of attack; notably, this is the internal space of the basement membrane, which encompasses the myelinated fibers [4]. These findings suggest the presence of local factors that differentiate between the nodal and internodal region [4]. One possible explanation may be the deposition of undiscovered antibodies on the peripheral nerves [4]. When the macrophages detect these antibodies, they activate, triggering myelin phagocytosis [4]. In fact, antibodies to a specific peripheral nerve glycolipid, sialosylneolactotetraosylceramide (LM1), were detected in cases with macrophages-induced demyelination [5]. Moreover, complement (C9) was also found on the myelin. In patients with Guillain-Barre syndrome (GBS), macrophage-induced demyelination is morphologically identical to patients with CIDP [6]. In the peripheral nervous system, foreign epitopes from infectious agents mimic the self epitope, which leads to autoantibody production [7]. This concept, molecular mimicry, has been proven in GBS [7]. A similar mechanism may indeed be responsible for the initial steps of the immunological process in CIDP [2]. However, studies have not yet shown a direct association between macrophages and autoantibodies apart from the study mentioned earlier [5]. Another emerging theory is that of IgG4 autoantibodies [2]. Studies have shown that in patients with CIPD, specific antibodies act on components of the nodes of Ranvier and paranodes [4]. Example of these IgG4 autoantibodies include anti-contactin-1 and anti-neurofascin-155 antibodies, which target the paranodal junction between axolemma and the myelin terminal loops [8]. Patients with these antibodies have been found to have distinct clinical features including tremor and sensory ataxia, as well as being unresponsive to intravenous immunoglobulin [9]. A sural nerve biopsy that contained anti-neurofascin-155 and anti-contactin-1 autoantibodies showed endoneural edema, decreased density of myelinated fibres due to axonal degradation, and a lack of cellular infiltration due to inflammation [10]. These observations are the basis for the alternative pathogenesis theory of CIPD [2].

CIDP can be divided into a "classical/typical" subtype and into atypical subtypes, of which there are many, suggesting that it is a spectrum of disease as classified by the European Federation of Neurological Societies/Peripheral Nerve Society Guidelines on the Management of CIDP (EFN/PNS) [11,12]. There are five main subtypes of CIDP; predominantly distal (distal acquired demyelinating symmetric [DADS]), asymmetrical (multifocal acquired demyelinating sensory and motor neuropathy [MADSAM]/Lewis-Sumner syndrome), focal, pure motor or pure sensory [12]. Clinically, it is imperative to distinguish between classical and atypical phenotypes of the disease as immunosuppressive drugs that are effective in typical CIDP demonstrate varying responses in atypical phenotypes [13]. Epidemiologically, only 51% of patients exhibit the classical phenotype [14]. Patients typically present with proximal and distal sensorimotor deficits with demyelination that is defined by the EFNS/PNS Criteria [12]. Pathologically, this definition includes vertical accumulation of Schwann cell cytoplasmic process, resulting in onion-bulb formation, segmental demyelination, and mononuclear cell infiltrates [15]. More specifically, macrophage-induced demyelination followed by remyelination is evident [3]. DADS is an IgM monoclonal protein associated neuropathy [15]. Clinically, DADS presents with a distal, symmetric sensory-predominant neuropathy that may cause sensory ataxia. Electrophysiology demonstrates abnormally increased distal latencies [16]. Although the accepted pathogenesis of classical CIDP and DADS is through macrophage-induced demyelination, recent studies also suggest that patients with autoantibodies against paranodal junction proteins—specifically contactin 1- and neurofascin 155-IgG4—may also present another mechanism by which immune-mediated neuropathies

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are manifested [3,15].

Sensory CIDP commonly presents as a diffuse sensory neuropathy with chronic progression. When it is restricted to sensory nerve roots, the phenotype is known as chronic immune sensory polyradiculopathy. In these cases, electrophysiology studies demonstrate normal motor nerve conduction velocities. First-line treatment for pure sensory CIDP is immunomodulatory therapy. Notably, it also responds well to IVIG or steroids. Therefore, the treatment of pure sensory CIDP is similar to that of classical CIDP [13]. However, while pure sensory CIDP itself responds to steroids, one study demonstrated that administration of high dose steroids in these specific cases may result in unfavorable outcomes. On the other hand, pure motor CIDP presents with motor deficits with normal sensory nerve conduction velocities [16,17]. In contrast to pure sensory CIDP, pure motor CIDP displays an unresponsiveness and even potential exacerbation of symptoms when treated with steroids [3]. Therefore, IVIG is recommended as first line [13]. Focal CIDP is the least common form of atypical CIDP, describing motor or sensorimotor neuropathy confined to one limb [12,13] Focal CIDP may involve nerve plexuses or one or more peripheral nerves in an upper or lower limb. Treatment of the focal phenotype of CIDP is immunomodulatory therapy that may require maintenance therapy [13].

Demyelinating neuropathies such as GBS and CIDP have been reported to be associated with haematological malignancies such as Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL). On the other hand, GBS and CIDP are rarely associated with solid tumours [18]. Within the literature, GBS and CIDP have been reported as a potential paraneoplastic neuropathy with carcinoma [19]. For example, Ayyappan et al. described the presentation of atypical CIDP, a distal acquired demyelinating symmetric (DADS), as a paraneoplastic syndrome in a 78-year-old female that was diagnosed with colorectal carcinoma only one month after being diagnosed with neuropathy. Her neuropathy was characterised by a 4-month history of distal motor and sensory involvement, which is typical of DADS. Nerve conduction studies confirmed a demyelination neuropathy that was consistent with the diagnosis of DADS neuropathy. Moreover, there was an elevated antinuclear antibody (ANA) titre, positive eosinophilia, and positive myelin-associated glycoprotein (MAG) IgM antibody by immunofluorescence essay. No treatment was established for her neuropathy due to its mild course. After endoscopic diagnosis of her colon adenocarcinoma and subsequent tumour resection, there was marked improvement of her clinical neuropathy. Follow up nerve conduction studies no longer revealed the demyelinating neuropathy and the laboratory studies returned a negative anti-MAG antibody and positive ANA. This study drew special attention to the importance of taking into consideration the paraneoplastic causes in patients diagnosed with subacute neuropathy [18]. Notably, there is the possibility that colon cancer and neuropathy may coexist by chance in this patient as colon cancer is not an uncommon condition. However, due to the clinical and electrophysiological remission of neuropathy following tumour removal, the study argued that this DADS neuropathy was very likely presenting as a paraneoplastic syndrome related to a tumour-associated immune response [18].

In another study, a similar patient was described with a 2-month history of acroparesthesias and distal muscle weakness [20]. Nerve conduction studies were consistent with demyelination. This patient received monthly IVIG for 42 months, with mild improvement. Post-therapy, the weakness worsened, and a reduced responsiveness to immune therapy was observed. To overcome this, IVIG was combined with steroids and plasmapheresis. However, this was also not effective. Ten months later, sigmoid colon adenocarcinoma was detected, which was duly treated with radical hemicolectomy followed by chemotherapy. Unfortunately, the patient died a year after their cancer diagnosis. The authors claimed that they were hesitant to consider this patient's DADS neuropathy as a paraneoplastic syndrome. There is thus an unmet need for large, randomised controlled trials regarding the subject to better elucidate the true aetiology.

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TA, MAN, YS: conceived the idea, designed the study, and drafted the manuscript.

TK, KY, AK: conducted literature search and created the illustrations.

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TA and EMA: revised the final version of the manuscript critically and gave the final approval.

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