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Narrative Review

Updated Review and Treatment Recommendations on Paraneoplastic Neurologic Syndromes and Chronic Pain

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Background: This comprehensive review of pain in paraneoplastic neurological syndromes focuses on current mechanisms that lead to pain, including autoimmune processes as well as the systemic secretion of factors that sensitize nociceptive nerves. Systemic secretion of functional molecules is a well-recognized phenomenon in endocrine paraneoplastic syndromes; however, cancer pain research has predominantly focused on cytokine-nerve interactions in the tumor microenvironment, and few groups have applied the molecular mechanisms of local pain to study widespread neuropathic pain resulting from systemic secretion. We present a novel perspective in the field of pain research by converging data from clinical oncology with recent molecular pain research on cytokine-mediated sensitization of nociceptive nerves.

Objective: Our objective was to conduct a review of paraneoplastic neurological syndromes and provide updates on therapeutic recommendations.

Study Design: We used a narrative review design.

Methods: This review was done using searches of PubMed, MEDLINE/OVID, SCOPUS, and manual searches of the bibliographies of known primary and review articles from inception to the present date. Other data sources included hand searches of publications driven by manuscript authors. Search terms included concepts of paraneoplastic syndrome and chronic pain with emphasis on both preclinical and clinical studies.

Results: Articles were screened by title, abstract, and full article review. They were then analyzed by specific clinical indications and appropriate data was presented based on critical analysis of those articles.

Limitations: More studies that distinguish autoimmune paraneoplastic pain syndromes from those related to systemic cytokine secretion are required.

Conclusion: By providing a unified review across disciplines, we illustrate that neuropathic pain related to the systemic secretion of cytokines may represent another category of paraneoplastic neurological syndromes distinct from the well-known autoimmune neuronopathies. In addition, we discuss the clinical significance of distinguishing autoimmune paraneoplastic pain syndromes from those related to systemic cytokine secretion and highlight the need for further research at the intersection of these fields. This review takes a look at both past and current literature with a critical analysis of findings and respective recommendations. In addition, based on review of the literature we provide updated therapeutic recommendations for the consideration of pain practitioners when dealing with this patient population.

Keywords: Paraneoplastic neurologic syndromes, chronic pain, neuropathic pain, treatment guidelines, cytokines

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Paraneoplastic syndromes are disorders that arise in the context of neoplasms but are not caused by tumor metastasis, invasion, or cancer treatment (1). Paraneoplastic syndromes can be broadly categorized as neurological, dermatological, hematological, endocrine, or rheumatological, depending on the tissues affected (1,2). Although rare, paraneoplastic syndromes occur most frequently in the background of small-cell lung cancer (SCLC), neuroendocrine tumors, thymomas, lymphomas, ovarian cancer, and breast cancer, with varying incidence depending on syndrome and tumor type (1).

Paraneoplastic neurological syndromes (PNS) are a subset of paraneoplastic syndromes that lead to neurological dysfunction and occur with an incidence of 3.1 cases per million-person-years in the general population and 0.25% to 3% at tertiary care referral centers (3). PNS can present with pain, weakness, sensory abnormalities, ataxia, dysautonomia, or central dysfunction (4). Although this review focuses on pain-related syndromes, other significant PNS include paraneoplastic cerebellar degeneration, paraneoplastic limbic encephalitis, Lambert-Eaton myasthenic syndrome, and anti-NMDAR encephalitis (1,5). While most forms of PNS occur with an incidence of less than 1%, Lambert-Eaton myasthenic syndrome (LEMS) and myasthenia gravis (MG) are among the more common, with LEMS presenting in 3% of patients with SCLC and MG developing in up to 33% of patients with a thymoma (6).

PNS can present in the setting of an occult cancer, and in 50% to 80% of PNS cases, neurological symptoms appeared prior to detection of cancer (3). Pain resulting from PNS occurs by heterogenous mechanisms and varies accordingly in its quality and sensitivity to treatment. Predominantly an autoimmune process, the pathogenesis of PNS entails immune recognition of neural antigens expressed in tumor cells and subsequent activation against neural tissue expressing the onco-antigens (4). Although activation of both humoral and cellular branches has been detected, neuropathy results primarily from cell-mediated damage to either peripheral nerves or dorsal root ganglia and does not appear to involve pathogenic antibodies (4).

Another important but seldomly addressed source of paraneoplastic pain involves the sensitization of nociceptive nerves by secreted factors, including both tumor-derived factors and those secreted by tissues in response to the presence of a tumor (7). Although this mediator-dependent process is distinct from the autoimmune pathophysiology commonly associated with PNS, syndromes arising from the release of these factors are best characterized as paraneoplastic due to their dependence on the delocalized, nonmetastatic effects of a neoplasm. While the interplay between tumor-derived factors and pain is typically investigated and discussed under the broad category of cancer pain, pain resulting from either secreted factors or autoimmunity hinges on the remote effects of the tumor. Therefore, both distinct processes fulfill the original descriptive criteria for PNS (8). Despite their separate treatment in the field, we discuss them together to illustrate the clinical value of distinguishing their mechanisms and presentations.

Pain arising from PNS is significant from both diagnostic and clinical perspectives, as it can either precede the diagnosis of a cancer or dominate the clinical picture after diagnosis (9). For these reasons, we provide a unified review of the diverse mechanisms behind PNS that result in pain and discuss the current state of treatment options.

Methods

This review was done using searches of PubMed, MEDLINE/OVID, SCOPUS, and manual searches of the bibliographies of known primary and review articles from inception to the present date. Other data included the results of hand searches of publications driven by manuscript authors. Search terms included concepts of paraneoplastic syndrome and chronic pain with emphasis on both preclinical and clinical studies. Due to the limited scope of studies with meta-analysis, clinical heterogeneity, and methodological diversity, we felt that a large scale meta-analysis would have limited scope and value to readers and have chosen to present the data as a comprehensive review.

Results

Categories of Painful Neuropathies

Subacute Sensory Neuropathy

Patients with paraneoplastic polyneuropathies fall broadly into 2 symptom-based categories: those with severe sensory ataxias and those experiencing dysesthesias and hyperalgesia (10). Although the focus of this review falls in the latter category of patients, it should be noted that both presentations occur along a continuum, and nearly all patients present with some degree of the subdominant symptom (10). Pain-dominated paraneoplastic neuropathies occur

with subacute onset and present with features of allodynia and severe mechanical hyperalgesia (10). Often, symptoms from sensory neuronopathies appear prior to the detection of a malignancy, and a range of 0.5 to 62 months of symptoms has been documented prior to the diagnosis with cancer (11). In a comparative study of patients presenting with either ataxia or neuropathic pain, sural nerve biopsies revealed a distinct pattern relating the dominant symptom at presentation and histological fiber pathology (10). Biopsies from patients with sensory ataxia revealed significant loss of large myelinated fibers with some degree of small myelinated fiber destruction (10). In contrast, the biopsies from patients presenting with significant pain and minimal ataxic symptoms were remarkable for loss of both small myelinated fibers and small unmyelinated fibers and the preservation of large myelinated fibers (10). The process guiding selective destruction of fiber type and diameter is unknown and cannot be distinguished by onconeural antibody, underlying malignancy, or treatment history (10).

POEMS Syndrome

POEMS syndrome is a rare disorder that arises in the context of plasma cell dyscrasias, primarily osteosclerotic myeloma and multicentric Castleman's disease (12,13). It presents as a constellation of polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (13). Because these clinicopathological features develop in the setting of a malignancy, POEMS syndrome is categorized as a paraneoplastic condition; however, the pathological changes are atypical of other paraneoplastic neuronopathies (12). Rather than an autoimmune polyneuropathy, POEMS syndrome is associated with a distinctive cytokine profile with elevated interleukin 1β (IL-1β), interleukin 6 (IL-6), tumor necrosis factor α (TNF-α), and VEGF (vascular endothelial growth factor), thought to contribute to the pathogenesis (12). Interestingly, IL-1β, IL-6, and TNF-α are also known mediators of hyperalgesia and will be discussed subsequently for their role as tumor-derived factors that sensitize nociceptive nerves (14-18). The dominant clinical feature of POEMS syndrome is painful polyneuropathy and, along with the diagnosis of a plasma cell dyscrasia, constitutes a required diagnostic criterion for the syndrome (19). POEMS syndrome causes a symmetric demyelinating polyneuropathy and is characterized by distal hyperalgesia, paresthesia, allodynia, spontaneous pain the lower extremities, and can be accompanied by autonomic dysfunction (13).

Secreted and Tumor-Derived Mediators

Identification of tumor-derived mediators and their systemic effects is a burgeoning area of cancer research. Abnormally elevated serum concentrations of TNF-α, for instance, have been identified in at least 8 different cancers including melanoma, non-small cell lung cancer (NSCLC), chronic lymphocytic leukemia, non-Hodgkin lymphoma, breast cancer, prostate cancer, colorectal cancer, and gastric cancer (20). A systematic review of cytokine patterns across cancers reports that elevated TNF- contributes to a recurring cytokine profile that likely modulates the host immune response in favor of tumorigenesis (20). Authors of the review propose that this cytokine profile functions as a maladaptive paraneoplastic syndrome at the core of many cancers and holds both prognostic and therapeutic implications (20). Other studies have shown that cytokine profiles are dynamic and shift with disease progression in a way that correlates with pain. In the case of breast cancer, distinct patterns of cytokines have been identified at early and advanced stages of the disease (21). Advanced cancer with significant pain has a strong association with elevated serum TNF-α and IL-1β (21). In contrast, early and relatively asymptomatic disease states tend to correlate with reduced levels of TNF-α and reduced IL-12 (21).

Pain Secondary to Other Paraneoplastic Syndromes

Nonneurological paraneoplastic syndromes can precipitate painful disorders secondarily. Rheumatological paraneoplastic syndromes including polymyalgia rheumatica (PMR), leukocytoclastic vasculitis, and hypertrophic osteoarthropathy are of particular relevance to the pain practitioner (22).

Polymyalgia rheumatica is an autoimmune condition characterized by pain and stiffness in the shoulder and hip girdles. Typically an autoimmune condition in the elderly, its paraneoplastic form can present in patients as pain before an underlying cancer declares itself (23,24). PMR is associated with hematological cancers, particularly leukemias and lymphomas, as well as cancers of the breast, lung, colon, kidney, and prostate (22).

Leukocytoclastic vasculitis is an inflammatory condition of small vessels in the skin (22,25). A painful, burning, and intensely pruritic rash of raised purpura is classically seen on the lower extremities but also can appear on the face, trunk, and upper extremities (22,25). While leukocytoclastic vasculitis is idiopathic in the vast majority of cases, its paraneoplastic manifestations oc-

cur most frequently in multiple myeloma, non-Hodgkin lymphoma, colon, lung, and kidney cancers (22,25). The paraneoplastic pathogenesis of this disorder involves circulating tumor antigens that result in type III hypersensitivity reactions and subsequent complement fixation on small vessels (22).

In contrast to PMR and leukocytoclastic vasculitis, hypertrophic osteoarthropathy occurs as a paraneoplastic condition 90% of the time (22). Subperiosteal bone deposition along the shaft of the phalanges results in pain, joint swelling, and digital clubbing (22,26). A strong association exists between lung cancer and the development of hypertrophic osteoarthropathy, with an incidence in lung cancer ranging from 0.7% to 17% across studies (26). In most cases, symptoms begin to improve quickly after surgical resection of the tumor and pathogenesis is believed to be related to paraneoplastic secretion of growth-promoting factors including growth hormone, growth hormone-releasing hormone, endothelial growth factor, and platelet-derived growth factor (26).

Rarely, other pain-related conditions, such as cluster headaches and trigeminal neuropathic pain, may occur as paraneoplastic syndromes. Facial pain in the form of intractable cluster headaches has been documented as a first sign of nonmetastatic lung cancer (27). In a review of 32 patients, facial pain associated with nonmetastatic lung cancer presented on average 9 months prior to the detection of a tumor and was predominantly unilateral and ipsilateral with respect to the tumor (27). In one case study, the patient's refractory cluster headaches preceded diagnosis with NSCLC, resolved completely with resection and vagotomy, and returned upon relapse of the cancer (27). It is theorized that secretion of tumor necrosis factor and interleukin 1 may play a role in the development of paraneoplastic facial pain as these molecules are not only elevated in the setting of malignancy, but also implicated in the pathogenesis of non-cancer-related cluster headaches (27).

Trigeminal neuropathy, another variant of facial pain, presented as the first sign of an autoimmune paraneoplastic syndrome with an anti-Hu antibody signature (28). In a case of subacute onset trigeminal pain with normal brain magnetic resonance imaging (MRI), the work-up revealed anti-Hu antibodies and oligoclonal bands in the cerebrospinal fluid (CSF) in the absence of visible brainstem lesions. The involvement of the trigeminal cranial nerve led to diagnosis with Hu-associated brainstem encephalitis. Further imaging and biopsy led to the detection of SCLC (28).

Mechanisms of Hyperalgesia

Onconeural Antibodies and the Role of Autoimmunity

Antibodies to neural antigens expressed in tumor tissue are termed onconeural antibodies (4,29). Historically, specific onconeural antibodies were isolated from patients with PNS and were once considered to be key players in the pathogenesis of neuropathy (9). However, it is now understood that the potential for paraneoplastic antibodies to cause disease depends on the epitope's subcellular localization (4,9,29). In Lambert-Eaton myasthenic syndrome, for example, paraneoplastic antibodies cause weakness by neutralizing extracellular voltage-gated calcium channels in the neuromuscular junction (29). In contrast, oncoantibodies isolated from patients with pain-dominated PNS target intracellular proteins on sensory nerves or dorsal root ganglia, and substantial evidence refutes the direct pathogenic effect of these oncoantibodies (4,29). Although these antibodies to intracellular targets are not directly pathogenic, a strong correlation exists between their detection in patients with unexplained neuropathy and the discovery of an underlying malignancy (4). This correlation served as the basis for subsequent research on autoimmune mechanisms behind paraneoplastic neuropathy (4).

Among cases of subacute sensory neuronopathy, anti-Hu antibodies targeting neuronal nuclear proteins, and anti-CRMP5 antibodies specific to oligodendrocyte cytoplasmic proteins, are the most prevalent and occur mostly in the setting of SCLC (4). The HuD protein is normally expressed in the nuclei of neurons and neuroendocrine cells; however, it is induced in SCLC cells and presented via the major histocompatibility complex class 1 (MHC-I) (4,11). This leads to a presumed break in peripheral tolerance and subsequent cytotoxic T lymphocyte (CTL)-mediated damage to sensory nerves (11). This pathogenic model is supported by T-cell receptor analysis, the identification of oligoclonal CD45RO memory CTLs within sensory nerve lesions, and the presence of CD4(+) CD45RO HuD-reactive T cells in circulation (11,30,31).

A series of seminal studies in the early 1990s investigated whether prevalent onconeural antibodies contributed to the development of neuropathy in the context of SCLC. These experiments included passive transfer and direct intraventricular injection of anti-Yo antibodies, a frequently isolated onconeural antibody in cases of paraneoplastic cerebellar degeneration with SCLC, into rodents (32-34). Neither these experiments nor im-

munization with recombinant Yo protein reproduced pathologic changes in the recipient animals (32-34). Subsequent experiments addressed whether immunization with HuD DNA or HuD protein could directly trigger the pathogenic changes characteristic of PNS (35,36). Although the vaccines proved to be immunogenic, no neuropathology was identified by histology, and no clinical features of paraneoplastic syndromes were detected (36). While these experiments refute the causal role of onconeural antibodies in sensory neuronopathy, they are consistent with the current model of cell-mediated autoimmune damage (37). Presently, onconeural antibodies in patients with unexplained sensory neuropathy serve as markers of undiagnosed malignancies but are neither quantitatively tracked as indicators of disease burden nor targeted in treatment (38).

Regarding the prognostic value of onconeural antibodies, a retrospective study comparing HuD antibody titers in SCLC patients over time found no correlation between titer levels and cancer progression, remission, or stability of paraneoplastic symptoms (39). The authors posit that measuring Hu-specific T-cell activity could be a more meaningful clinical marker of PNS disease status, and some evidence exists that Hu-specific T-cell activity correlates with reduction in cancer burden (39).

Despite prior data arguing against the prognostic value of onconeural antibodies, a recent study published compelling findings of a 5-year survival advantage to patients seropositive for anti-CRMP5 oncoantibodies over those presenting with either anti-HuD antibodies or both (40). In addition to this prognostic insight, the autoantibodies correlated with distinct clinical presentations. Patients seropositive for anti-CRMP5 antibodies experienced higher prevalence of pain, asymmetric polyradiculopathy, and markers of CSF inflammation than those seropositive for anti-Hu antibodies (40). Whether the survival advantage and neuropathy coincide with a more robust immune response is speculative but intriguing.

While a prognostic relationship between oncoantibodies and clinical outcomes was not recognized in prior literature, distinct pain phenotypes have been previously documented. Antibodies against CRMP-5 were associated with damage to both the dorsal root ganglia and peripheral nerves (11,41). The corresponding clinical presentation is painful, asymmetric axonal polyradiculoneuropathy (29,40,41). In a retrospective comparative study of 105 patients with PNS neuropathy, Dubey et al found that moderate to severe neuropathic pain was more frequent in patients with CRMP-5 antibodies than Hu antibodies (40). However, patients with anti-Hu antibodies were significantly more likely to develop dysautonomia and were overall more likely to develop some form of subacute sensory neuronopathy (40).

In contrast to the well-characterized, nonpathogenic oncoantibodies isolated from patients with painful PNS, a case report from 2011 documents suspected pathogenic antibodies against the ganglionic neuronal acetylcholine receptor in a 62-year-old woman with previously undiagnosed SCLC and new-onset neuropathic pain (42). The patient presented with paresthesias of the hands, feet, and tongue but did not display any discernable dysautonomic symptoms (42). Although this was the first description of nACh receptor antibodies implicated in a paraneoplastic pain syndrome, the patient's nonlength-dependent sensory neuropathy in the context of SCLC is highly consistent with a diagnosis of PNS (42). Although speculative, this case may represent a rare scenario where onconeural antibodies mediate a pathogenic role and is supported by the identification of the α3 subunit of nACh receptors on dorsal root ganglia (42).

It should be noted that not all patients with tumors expressing paraneoplastic antigens, such as Hu or CRMP-5, develop autoreactive immune responses (29,41). In Yu et al's characterization of CRMP-5 paraneoplastic autoantibodies, only 2 of 14 patients with CRMP-5-expressing SCLC tumors tested seropositive for anti-CRMP-5 antibodies (41). This indicates that tumor presentation of neural antigens is not sufficient to generate autoimmunity (41). The conditions required to break immune tolerance remain unclear and are difficult to assess given the rarity of paraneoplastic syndromes. It is possible that specific cytokine milieus are required in addition to expression of onconeural antigens in order to initiate a paraneoplastic process (41). Yu et al propose that systemic interferon gamma (IFNγ) can cause upregulation of MHC-I on neurons and promote the CTL-mediated response (41). If a unique cytokine profile promoting this process can be identified, additional therapeutic options may become available.

Pathology in Dorsal Root Ganglia

Evidence for immune-mediated damage to the dorsal root ganglia (DRG) includes the detection of inflammatory cells within the endoneurium of DRG and peripheral nerves (10). In addition, cytotoxic T lymphocytes found within the capsule of satellite cells

were found to be in close contact with sensory neurons (11). In further support of the T-cell-mediated model of pathogenesis, patients with higher levels of CTL infiltration within their tumor more frequently developed painful paraneoplastic syndromes than individuals with reduced tumor infiltration (11).

With respect to the distribution of affected DRG, studies on sensory neuron action potential (SNAP) reduction reveal selective vulnerability to nerves originating from certain DRG (43). In particular, the DRG contributing to the peroneal nerve, as well as the ulnar and radial nerves, showed the greatest reduction in SNAPs (43). However, the time lapse to threshold values of SNAP reduction was similar for all nerves, and the authors conclude that the destructive process begins uniformly and progresses to different degrees depending on conditions within specific DRG (43). The precise conditions determining this selective vulnerability within certain DRG are unclear.

Peripheral Nerve Damage

There is significant evidence supporting CTL-mediated damage to the DRG as a primary cause of pain in paraneoplastic neuropathies. However, it is presumed that lesions to cell bodies in the DRG lead to downstream loss of small fibers in the periphery (10). Additionally, inflammatory cell infiltrates have been detected not only in DRG lesions of patients with the painful variant of PNS neuropathy, but also in their peripheral nerve endoneurium and epineural vessels (10). Peripheral nerve damage in painful PNS neuronopathies is hallmarked by axonal degeneration of small, myelinated and unmyelinated fibers (10).

POEMS syndrome shares the feature of injury to peripheral nerves, but it is marked by an unusual pattern of myelinated fibers loss with protection of unmyelinated fibers (10,13). Sural nerve biopsies from patients with hyperalgesia and POEMS syndrome reveal extensive edema in the endoneurium, dramatic reduction in the number and density of small myelinated fibers, and a modest reduction in large myelinated fibers. No significant injury or loss of unmyelinated fibers is detected (13). The authors remark that this histopathological pattern resembles the imbalance between C and Aδ nociceptive fibers described in post-herpetic neuralgia and normal cold hyperalgesia, where thinly-myelinated Aδ fibers serve to dampen pain transmission by unmyelinated C fibers (13,44). The mechanism for hyperalgesia in POEMS syndrome likely involves the selective destruction of inhibitory Aδ fibers, thereby permitting excessive nociceptive signaling to occur through the remaining unmyelinated C fibers (13). The underlying cause of small myelinated fiber loss has yet to be determined. However, it is speculated that the proinflammatory cytokine profile in POEMS syndrome may be related to pathological changes (12). Whether the relationship between proinflammatory cytokines and myelinated fiber loss is causal remains unclear. As Koike et al note, proinflammatory cytokines can be either the product of Schwann cell axonal degeneration or the cause of axonal degeneration if released systemically (13). What appears to be clear is that POEMS syndrome patients with myelinated fiber loss and hyperalgesia have proportionally elevated IL-6 levels (13).

Secreted and Tumor-Derived Mediators

While much existing research on tumor-derived factors and pain addresses local tumor-nerve interactions, reports of diffuse bone pain from patients receiving prophylactic granulocyte colony stimulating factor (G-CSF) injections such as filgrastim and lenograstrim surrounding chemotherapy speak to the possibility of widespread pain if such factors are secreted systemically by tumor cells (45). The molecular basis of sensory nerve sensitization, viewed alongside clinical observations of pain surrounding endogenous and exogenous exposures to these factors, provide a compelling reason to consider pain from secretions beyond the tumor microenvironment as a distinct PNS (37,45).

From a clinical perspective, a connection between systemic cytokine secretion and cancer pain was recognized by Amor et al in the case report of a patient with metastatic thyroid cancer who experienced severe leukocytosis and subacute peripheral neuropathy unrelated to tissue inflammation or cancer treatment. In the span of 4 weeks, the patient developed severe myeloid leukocytosis (103,100 WBC/mm^3) with coincident neuropathic pain characterized by allodynia and hyperalgesia (7). The patient's prior disease history was unremarkable for leukocytosis as white blood cell counts did not exceed 10,000 WBC/mm^3, and infectious causes of leukocytosis were ruled out. The patient's neuropathy developed in parallel with worsening leukocytosis, a pattern congruent with paraneoplastic secretion of G-CSF and granulocyte-macrophage colony-stimulating factor (GM-CSF) by tumor cells (7). Although myeloid-CSF levels were not directly measured, the temporal correlation between the patient's leukocytosis and neuropathic pain establishes a compelling case for

G-CSF and GM-CSF as common mediators of both his neuropathy and leukocytosis (7).

From a mechanistic standpoint, substantial molecular research has identified hematopoietic colony-stimulating factors as agents that sensitize nociceptive nerves (46). Schweizerhof et al identified receptors for hematopoietic colony-stimulating factors on sensory nerves in vivo and showed that these receptors are functionally capable of initiating STAT3 signal transduction on cultured DRG neurons (46). Downstream of signal transducer and activator of transcription 3 (STAT3) activation, cultured DRG neurons upregulated the expression of Na channel Nav1.8 and heat- and capsaicin-activated channel TRPV1, both important channels in hyperalgesia (46). Furthermore, subcutaneous injections of GM-CSF in mice potentiated pain in response to capsaicin challenge more than vector control injections, as measured by release of calcitonin gene-related peptide (CGRP), a pain-associated peptide (46). Of functional and therapeutic interest, neutralizing antibodies to G-CSF and GM-CSF receptors prevented hyperalgesia in mice models of sarcoma-pain (46). Together, these data present important mechanistic evidence that CSFs potentiate pain by sensitizing nociceptive fibers.

TNF-α has also been identified in the background of other paraneoplastic syndromes, such as paraneoplastic leukocytosis in the context of anaplastic large cell lymphoma (47). In a case study of 5 patients with a highly aggressive anaplastic large cell lymphoma and paraneoplastic leukocytosis, all were found to have elevated serum levels of G-CSF, and tumor tissue from 4 of the 5 patients stained positively for TNF-α (47). The production of G-CSF and TNF-α correlated with cases that developed paraneoplastic leukocytosis, and neither elevated G-CSF nor TNF-α tissue staining was detected in characteristic cases of anaplastic large cell lymphoma without paraneoplastic leukocytosis (47). Although authors note only intermittent diffuse abdominal pain among patients, the median survival of study participants was 3.5 weeks, and the patients' rapid disease progression may have masked a relationship between TNF-α secretion and development of neuropathic pain. Despite this limitation, the finding that TNF-α is produced by tumor cells in the context of a systemic paraneoplastic syndrome represents an important concept in pain research because it contributes to an expanding repertoire of tumor-derived molecules that are secondarily able to cause neuropathic pain.

Earlier literature implicated TNF-α in paraneoplastic states such as cachexia, hypercalcemia, and leukocytosis. However, in contrast to the direct staining of TNF-α described by the study above, prior work suggests a more subtle and indirect signaling interaction between tumor cells and remote tissues that ultimately leads to systemic secretion. In this pathway, tumor cells induce the release of TNF-α from distal tissues such as the spleen by the release of unidentified factors (48). Studies elucidating the origin of systemic TNF-α secretion were conducted on MH-85 cells, a cell line derived from human squamous cell carcinoma of the maxilla that characteristically triggers cachexia, hypercalcemia, and leukocytosis in a tumor-bearing mouse model (48). Nude mice bearing MH-85 tumors displayed predictable features of cachexia, hypercalcemia, and leukocytosis and were found to express TNF-α at 4 times the level of control animals (48). The administration of polyclonal anti-TNF-α antisera dramatically improved all 3 pathological parameters. Despite the functional role of TNF-α in this paraneoplastic syndrome, the factor was undetected in the supernatant of cultured MH-85 cells. The transfer of tumor-conditioned media, however, to mouse splenocytes of the macrophage lineage resulted in release of TNF-α from host cells (48). Furthermore, either splenectomy or intravenous infusion of normal splenocytes was sufficient to potently normalize serum calcium values, WBC counts, and animal weight. The authors conclude that signaling molecules released by tumor cells induce the paraneoplastic secretion of factors, such as TNF-α, from host tissues (48). The body's indirect response to neoplasms represents an alternative pathway by which paraneoplastic syndromes can arise and increase the systemic levels of a pleiotropic factor.

The pleiotropic effects of TNF-α include not only constitutional symptoms when released systemically but also neuropathic pain. The pathologic link between TNF-α and mechanical allodynia was established by a comparative study of sural nerve biopsies from patients with painful and nonpainful neuropathies of inflammatory origin (15). Biopsies from patients with mechanical allodynia revealed up-regulation of TNF-α in Schwann cells and increased concentrations of serum-soluble TNF-α receptor relative to biopsies from nonpainful forms of neuropathy (15). These experiments expanded on prior work demonstrating the involvement of TNF-α in ectopic nociceptive signaling and peripheral hyperalgesia, coupled with the finding that anti-TNF-α and anti-IL-6 antibodies ameliorate neuropathic pain (10,15,17,49,50). Furthermore, TNF-α has been impli-

cated in other pain conditions such as chronic regional pain syndrome (CRPS) (10). In a study comparing plasma concentrations of soluble TNF-α receptor (sTNF-RI) among CRPS patients with and without mechanical hyperalgesia, serum sTNF-RI levels were significantly higher in patients experiencing mechanical hyperalgesia than those of controls or CRPS patients without hyperalgesia.

In fact, it has been speculated that TNF-α as well as other cytokines released by invasive immune cells in the DRG contribute to neuropathic pain in the autoimmune models of PNS (10). It would then follow that either direct release of TNF-α by tumor cells or systemic secretion by host tissues could elicit neuropathic pain.

IL-6 is similar to TNF-α in that its pleiotropic effects straddle both the fields of molecular pain research and paraneoplastic syndromes. Elevated serum IL-6 has been consistently reported in over 13 distinct cancers and correlates with poor prognostic outcomes (20,51). Systemic secretion of IL-6 results in paraneoplastic syndromes related to those of TNF-α, including immune dysregulation, osteoporosis, and cachexia (52).

Secretion of IL-6 and its soluble receptor allow tissues that normally do not participate in classical IL-6 signaling to respond with diverse systemic effects (16). From the pain perspective, elevated expressions of IL-6 and its receptor have been detected in the spinal cord and DRG of pathological pain models, including cancer pain and neuropathic pain (16). Consequences of signaling lead to sensitization of nociceptive C fibers, hyperalgesia, and allodynia (53). In rat models of neuropathic pain, increasing levels of IL-6 are detected in the substantia gelatinosa and motor neurons following singular peripheral nerve injury by sciatic cryoneurolysis (14). When recombinant human IL-6 was delivered intrathecally, lesioned rats developed signs of thermal hyperalgesia and their nonlesioned counterparts exhibited mechanical allodynia (14). Furthermore, intrathecal administration of anti-IL-6 antibodies has been shown to reduce pain behaviors in model animals and provides encouraging data for the use of existing humanized monoclonal antibodies against IL-6 or the IL-6 receptor as an additional treatment option (16).

A growing number of molecules similarly participate in pathological pain and paraneoplastic syndromes and would merit investigation from a multidisciplinary perspective. They include IL-1β, which was among the first cytokines implicated in cancer pain and has been shown to mediate local pain signaling by inducing prostaglandin production (18). IL-1β is secreted along with IL-6, TNF-α, and other pro-inflammatory cytokines in various cancers and produces similar features of pathological pain. Despite their diverse physiological functions in health, secretion of proinflammatory cytokines, CCL2, nerve growth factor, and various cyclooxygenase 2 products have all been implicated in neuropathic and cancer-related pain (54-62).

Disease Course of Autoimmune Paraneoplastic Neuropathy

Expanding on the immunological basis of PNS, a study by Psimaras et al evaluated clinical data in CSF samples from 295 patients in the European PNS database from 2000 to 2007 (63). Authors identified pleiocytosis and/or other indicators of CSF inflammation in 93% of patients presenting with paraneoplastic neurologic symptoms and serum-positive for onconeural antibodies (63). Importantly, the data demonstrate a subacute inflammatory phase spanning the first 3 months of symptoms, which likely coincides with marked neuronal loss, and is followed by a stable phase with poor clinical improvement (63).

This model of disease phase-specific immune damage is supported by a retrospective study of SNAPs on patients with paraneoplastic sensory neuropathies (43). SNAP reduction was measured as a surrogate marker for neural loss within DRG and was assessed at different time points after symptom onset. The data recreated a monophasic distribution of pathological changes, where peak SNAP reduction occurred 2 months after the onset of symptoms and stabilized by 7 to 10 months post symptom onset (43). Together, these studies suggest that the immunological events leading to neuropathic symptoms follow a subacute time course (43,63). Given the time-dependence of tissue damage, the onset of symptoms marks a finite period of treatment sensitivity. After this therapeutic window, symptoms from irreversible tissue damage are largely refractory to treatment (43,63).

Updated Literature on Treatment Recommendations

Due to the rarity of paraneoplastic syndromes, few controlled studies on treatment are available (64). However, treatment approaches can be broadly categorized by whether the underlying mechanism involves immune activation against intracellular or extracellular antigens. In contrast to paraneoplastic disorders involving pathogenic antibodies against extracellular antigens,

as in the case of Lambert-Eaton myasthenic syndrome, the disorders discussed in this review occur primarily by T-cell-mediated responses against intracellular antigens and are unlikely to respond to treatment with intravenous immunoglobulin IVIg and rituximab (64). Recent analysis of patients with painful axonal polyradiculopathy and seropositivity for anti-CRMP5 and anti-HuD antibodies revealed significant pain reduction and symptom stabilization with high-dose IV corticosteroid treatment and high-dose oral prednisone (40). In contrast with older recommendations that emphasize symptom management by targeting underlying malignancy, painful neuropathy in this cohort failed to improve with surgical or chemotherapeutic treatment of the cancer; instead, symptom improvement was attributed exclusively to high-dose immunomodulators (40).

First-line neuropathic pain medications such as gabapentin, pregabalin, amitriptyline, duloxetine, and venlafaxine can be used for symptomatic treatment, but they present limited efficacy without control of the underlying malignancy (64). As previously described, Psimaras' finding that inflammatory damage to neural tissue is monophasic suggests that early therapeutic intervention, within the first few weeks to months, may be the most sensitive period for preventing irreversible neuronal damage (63).

Interestingly, Broekhoven et al speculated that the Th1-mediated autoimmune response presumed to cause paraneoplastic neuropathy in patients with anti-Hu antibodies may be amenable to treatment with human chorionic gonadotropin (65). The basis of this study was the observation that Th-1-mediated autoimmune diseases, such as rheumatoid arthritis and multiple sclerosis, often improve over the course of a pregnancy (65). The study included 15 patients seropositive for anti-Hu antibodies presenting with subacute neuropathy and entailed the intramuscular injection of 10,000 IU of hCG over the span of 12 weeks. Although the study was uncontrolled and unblinded, the authors report either functional improvement or stabilization in 47% of the patients based on the modified Rankin Scale, as well as significant neurological improvement in 27% of patients as evaluated by Edinburgh Functional Impairment Tests. Despite the limited scope of the study, further investigation of hCG in the treatment of painful paraneoplastic neuropathies is compelling given the paucity of effective treatment options following symptom onset.

With respect to paraneoplastic secretion of cytokines and other compounds that promote neuropathic pain, the use of existing antagonists may be of clinical value; however, the direct use of these drugs for the treatment of pain has not been formally evaluated (18). IL-6 antagonists represent one such promising category. A humanized monoclonal antibody targeting the IL-6 receptor, tocilizumab, is currently used for the treatment of moderate to severe rheumatoid arthritis and juvenile idiopathic arthritis (18). Importantly, tocilizumab has been periodically reported to improve paraneoplastic cachexia and could therefore be of great value in the treatment of pain resulting from paraneoplastic secretion of IL-6 (18,66,67). While IL-6 antiserum has been effective in reducing pain in animal models, no direct human studies addressing pain have yet been conducted.

TNF-α antagonists also show promise in the reduction of paraneoplastic syndromes including cachexia, fatigue, and other constitutional symptoms; and the efficacy of anti-TNF-α biologics in the treatment of systemic inflammatory conditions such as rheumatoid arthritis has already been established (18). Like tocililizumab, TNF-α antagonists may be effective in the treatment of widespread cancer pain; however, here as well there is a deficit of clinical studies evaluating these drugs in the context of cancer pain (18).

In the case of POEMS syndrome, a paraneoplastic syndrome associated with multicentric Castleman disease (MCD), immune dysregulation and the overproduction of proinflammatory cytokines lead to systemic inflammation and neuropathic pain (12). Recent reports document the successful treatment of MCD with anakinra, an IL-1 receptor antagonist (68). This treatment strategy has gained attention not only for its efficacy in treating refractory MCD, but also for the dramatic and rapid improvement of paraneoplastic signs such as fatigue and anorexia in the span of one week (68). As additional cases of treatment with anakinra are documented, we predict POEMS syndrome-associated polyneuropathy will improve not only due to treatment of the underlying malignancy but also by antagonism to the pro-nociceptive effects of IL-1.

Discussion/Conclusion

Paraneoplastic syndromes are indirect systemic consequences of neoplasms and are not caused directly by metastasis, invasion, or cancer treatment (8). PNS constitute a class of paraneoplastic syndromes that specifically result in damage to the nervous system and can present as diverse manifestations of neurological damage (1). Although PNS are rare, the most prevalent

neurological signs include neuropathic pain, sensory ataxia, and motor weakness (69). Subacute sensory neuropathy often precedes detection of a malignancy, and the onset of symptoms prior to cancer diagnosis can vary from less than one month to 5 years (10,11) The onset of paraneoplastic pain is therefore significant from both diagnostic and clinical perspectives.

Paraneoplastic subacute sensory neuropathy is often accompanied by the presence of onconeural antibodies, the most common of which are anti-HuD and anti-CRMP5, occurring predominantly in the context of SCLC, thymomas, and gynecological cancers (4,29,41,69). These antibodies are significant diagnostically; however, they do not directly participate in the pathogenic development of neuropathy (38,39). Traditionally, the clinical value of onconeural antibodies was limited to aiding diagnosis, as they are poor markers of clinical response (39). However, recent data reveals a more nuanced perspective of their clinical value. Specific onconeural antibodies appear to correlate with a greater propensity for neuropathic pain, as in the case of anti-CRMP5 antibodies (40). However, anti-CRMP5 antibodies are also linked with a 5-year survival advantage over patients seropositive for anti-HuD antibodies (40). This relationship, if confirmed, may be explained by a more robust immune response to tumor tissue, but this hypothesis remains speculative to date (40). Ultimately, the controversy over the prognostic value of onconeural antibodies will need to be resolved with additional studies.

The current model explaining neuropathic pain resulting from PNS is based on autoimmune Th1-mediated cytotoxic damage to the DRG and peripheral nerves (4,9,11). The conditions for breaking peripheral tolerance to neural antigens expressed on tumor tissue are currently unclear but may be a consequence of increased IFN-γ secretion and subsequent upregulation of MHC-I on neural tissue (41).

PNS resulting from autoimmune etiology are difficult to treat after damage to neural tissue has occurred (63). A monophasic period of autoimmune damage has been proposed and marks a finite window for therapeutic intervention (63). Treatment of the underlying malignancy is of highest priority for the control of PNS; however, additional immunomodulatory interventions may be efficacious if applied within that early window (63).

Another important consideration is the possibility of triggering autoimmune conditions similar to PNS with the use of immunomodulatory cancer treatments, such as ipilimumab, a CTLA-4 checkpoint inhibitor (70,71). A recent study reported cerebellar Purkinje cell death in a mouse model of CTLA-4 blockade-induced PNS, and authors caution against the use of ipilimumab and other immune modulators in cancers of an ectodermal origin (70). While from a clinical perspective the risk of triggering PNS is likely outweighed by the therapeutic promise of immunotherapy, the CTLA-4 blockade-induced PNS mouse model may prove valuable in understanding how immune tolerance is broken in unprovoked cases of autoimmune PNS (71). Although PNS are very rare, the prevalence of autoimmune neurological syndromes resembling spontaneous cases of painful PNS may increase with the use of novel cancer immunotherapies.

In contrast to autoimmune models of PNS, paraneoplastic secretion of compounds that sensitize nociceptive nerves by tumor cells or distal tissues represents another important, albeit more rare form of painful PNS (7,12,18,20). Paraneoplastic secretion of cytokines and other tumor-derived factors is well-documented for hematological and endocrine malignancies as well as for solid tumors of the lung, kidney, gastrointestinal, breast, and genitourinary tract (47). Secretion of functional molecules can either occur directly by tumors or by remote tissues in response to a tumor. In the case of tumor-derived factors, autocrine secretion of cytokines stimulates growth-promoting pathways and creates an immuno-evasive environment for tumors, making cytokine antagonists an attractive target for drug development (51,72-74). Along with the promitotic and immunomodulatory effects of secretion, a variety of paraneoplastic conditions coincide with cytokine release from tumors, most notably cachexia, anorexia, fever, hypercalcemia, and osteoporosis (74). In the literature, both basic science and clinical case reports anticipate that investigational cytokine antagonists will reduce tumor load as well as improve constitutional symptoms (73,74). At the same time, substantial work in the field of pain research has established cytokines and other tumor-derived factors as agents that sensitize nociceptive nerves, causing allodynia and hyperalgesia (75). Cytokine secretion within the tumor microenvironment has become a recognized source of cancer pain, and cytokine antagonists have succeeded in reducing pain scores in animal models (18). However, despite the body of work dedicated to understanding the role of local mediators in pain perception, very few groups have directly analyzed neuropathic pain as a consequence of systemic secretion. The intersection of mechanistic

pain research and paraneoplastic syndromes that result from systemic secretion remains an important niche to be filled in the field of cancer pain research.

The most evident clinical example comes from a case report of coincident paraneoplastic leukocytosis and severe subacute peripheral neuropathy refractory to conventional neuropathic pain treatment (7). The authors of this report hypothesize the secretion of myeloid colony-stimulating factors as a common paraneoplastic origin of both leukocytosis and neuropathic pain (7). While this report represents a compelling case for cytokine-mediated paraneoplastic pain syndromes, many areas remain open for future research. It will be important to assess the frequency of allodynia and hyperalgesia among patients who develop paraneoplastic leukocytosis in addition to documenting the corresponding serum concentrations of colony-stimulating factors and other cytokines to establish potential dose-dependent effects and duration.

While elevated serum levels of proinflammatory cytokines and other known nociceptive agents have been described in various paraneoplastic syndromes, there is a deficit of research dedicated to directly studying the intersection of these 2 fields (12,18,20,48). The clinical value of distinguishing painful PNS on the basis of autoimmune or secreted etiologies is that the treatment options and therapeutic windows vary accordingly (63,64). While autoimmune PNS are characteristically refractory to pain treatment once tissue damage has occurred, cytokine-mediated syndromes may still be amenable to intervention (63). Chimeric and humanized monoclonal antagonists to proinflammatory cytokines such as TNF-, IL-6, and IL-1β have been in use clinically for inflammatory disorders and occasionally for the treatment of constitutional paraneoplastic syndromes; however, their ability to mitigate cancer pain has not been directly assessed in clinical trials despite substantial preclinical evidence supporting the role of proinflammatory cytokines in hyperalgesia and allodynia (7,18,52,67,68). Research on cytokine antagonists for the purpose of pain treatment may therefore be relevant to both rare cases of PNS pain and more frequently occurring localized cancer pain. While the intrinsic risk of infections and worsened oncological outcomes with cytokine antagonists is a concern that must be carefully addressed, the precedent use of proinflammatory cytokine antagonists in improving paraneoplastic constitutional symptoms suggests the risk may be manageable and worth investigating. Furthermore, paraneoplastic secretion of nociceptive factors could be of particular relevance in the subset of paraneoplastic pain cases where no onconeural antibodies are detected (8,38).

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