Review Article

Paraneoplastic syndromes in lung cancer and their management

Asad Anwar[1], Firas Jafri[1], Sara Ashraf[2], Mohammad Ali S. Jafri[3], Michael Fanucchi[3]

[1]Department of Internal Medicine, Westchester Medical Center, Valhalla, NY, USA; [2]Department of Hematology/Oncology, Marshall University, Huntington, WV, USA; [3]Department of Hematology/Oncology, Westchester Medical Center, Valhalla, NY, USA

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Correspondence to: Mohammad Ali S. Jafri, MD. Department of Hematology/Oncology, Westchester Medical Center, Valhalla, NY, USA.
Email: mohammad.jafri@wmchealth.org.

Abstract: Paraneoplastic syndromes are most frequently associated with lung cancer. This review considers a variety paraneoplastic syndromes associated with lung cancer and discusses their pathophysiology, clinical features and management options.

Keywords: Paraneoplastic syndromes; lung cancer; thoracic oncology

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Introduction

Paraneoplastic syndromes refer to the remote effects associated with malignancy which are unrelated to direct tumor invasion or metastases (1). These may occur before the cancer is diagnosed and can be independent in their severity to the stage of the primary tumor. Paraneoplastic syndromes are most commonly associated with lung cancer, reported in approximately 10% of cases (1). Endocrine syndromes, particularly syndrome of inappropriate ADH secretion (SIADH) and humoral hypercalcemia of malignancy (HHM) are the most common paraneoplastic syndromes seen in lung cancer and are related to the histologic type of cancer (1). This review considers a variety of paraneoplastic syndromes associated with lung cancer and discusses their pathophysiology, clinical features and management options.

Endocrine syndromes

Hypercalcemia

Hypercalcemia has been reported in 2–6% lung cancer patients at the time of initial diagnosis; the incidence increases to 8–12% over the disease course (2). It is associated with a poor prognosis. When associated with PTHrP production (parathyroid hormone related-protein), it is referred to as HHM.

HHM is observed in a variety of malignancies such as breast, renal, multiple myeloma and lung; squamous cell is the most frequently observed subtype (3-5). Osteolytic metastases are another significant cause of hypercalcemia in malignancy.

Of the four mechanism of hypercalcemia secondary to HHM (secretion of PTHrP, parathyroid hormone, 1-25 dihydroxy vitamin D or granulocyte colony stimulating factor), secretion of parathyroid hormone related protein is the most common in lung cancer. Parathyroid hormone production is reported as a rare mechanism (6). Chronic G-CSF exposure promotes osteoclastic bone resorption (7).

HHM is typically found in advanced disease and is associated with a poor prognosis (7). The clinical features of hypercalcemia are variable and can be non-specific; gastrointestinal symptoms (such as nausea, vomiting abdominal pain and constipation) are common. Dehydration (vomiting, polyuria) in the setting of hypercalcemia can result in renal dysfunction (3-5). Neuropsychiatric manifestations range from fatigue and lethargy to changes in mood and cognitive dysfunction (3-5).

Diagnostic evaluation should ideally ionized calcium measurement in addition to PTH levels. However, if

ionized calcium levels are not available, then calcium and albumin levels should be measured at the same time and calcium levels should be corrected for albumin levels. As for most paraneoplastic endocrine syndromes, treatment of the underlying malignancy is the most successful treatment strategy (3). Acute hypercalcemia is managed with intravenous fluid administration (3) with frequent monitoring of calcium levels. Loop decrease calcium reabsorption and can be added after adequate fluid resuscitation. Bisphosphonates are another useful treatment option due to their inhibitory effects on bone resorption (3). Calcitonin also suppresses bone resorption and is useful in the short term (4,5). Denosumab binds to RANKL to prevent ligand interaction with RANK receptors on precursor osteoclasts which interferes with osteoclast maturation and survival (8). It prevents skeletal-related events in patients with bone metastases and is a generally well-tolerated treatment (9).

SIADH

SIADH represents a state of euvolemic, hypoosmolar hyponatremia, which, in the case of lung cancer is secondary to ectopic ADH production; 10–45% of small cell lung cancer (compared to 1% of non-small lung cancers) can produce ectopic ADH (10,11) resulting in excessive urinary sodium excretion. Hypothyroidism, volume depletion and adrenal insufficiency should be excluded. Although the stage of SCLC does not seem to affect the occurrence of SIADH, hyponatremia tends to worsen prognosis in comparison to normal sodium levels in these patients (12). The symptoms of SIADH depend on the degree and acuity of the hyponatremia. Non-specific symptoms such as headache and fatigue might be the initial presentation of paraneoplastic SIADH. Acute (<48 hours), severe (serum sodium <120 meq/L) hyponatremia leads to cerebral edema causing altered mental status, seizures and death. Chronic, mild to moderate, hyponatremia may not produce any significant neurologic symptoms.

Definitive management of paraneoplastic SIADH involves treatment of the malignancy itself. Chemotherapy for SCLC can mitigate and in several cases resolve SIADH in at least 80% of patients in some studies (4). Recurrence of SIADH can be related to tumor recurrence or progression (13). Beyond treatment of the cancer, paraneoplastic SIADH is managed largely in the same way as it is in patients without cancer.

In acute, severe hyponatremia, particularly with neurologic symptoms, hypertonic saline is administered. Rapid overcorrection is avoided because of the risk of osmotic demyelination. In milder, asymptomatic cases, free water restriction (1 L/day) is the first step. Pharmacologic treatments may be employed if conservative measures fail to produce an adequate response. Demeclocycline, a tetracycline antibiotic, decreases renal response to ADH and has been used to manage SIADH. Vasopressin receptor antagonists (conivaptan, tolvaptan) increase urinary free water excretion and have also been shown to be effective.

Ectopic Cushing's syndrome (ECS)

The manifestations of ECS result from the unregulated production of adrenocorticotropic hormone (ACTH) from malignant cells (4). Elevated ACTH levels may be detectable in up to 50% of patients with lung cancer (13,14). Ectopic ACTH secretion is almost always associated with SCLC (14) or less commonly bronchial carcinoids. About 30% of all cases of SCLC are associated with ectopic hypersecretion of ACTH (15), and this tends to confer a worse prognosis (16).

ACTH stimulates the adrenal production of glucocorticoids (17). Hypercortisolism results in hypokalemic metabolic alkalosis and secondary hypertension that is difficult to treat. Hyperglycemia is also common (18,19). Characteristic findings on physical examination include abnormal fat deposition (moon facies, buffalo hump, centripetal obesity) and violaceous striae (20).

The diagnosis of ECS requires the exclusion of iatrogenic hypercortisolism from exogenous steroids (21). Initial work-up of hypercortisolism includes measurements of late-night salivary cortisol, 24-hour urinary cortisol and the 1mg overnight dexamethasone suppression test. If results suggest hypercortisolism, an ACTH level can distinguish Cushing's from ECS (22). The absence of a pituitary tumor on imaging (CT, MRI) with an elevated morning ACTH raises the suspicion of ECS. High-dose dexamethasone will suppress a pituitary but not an ectopic source of ACTH.

In most cases, treatment of the underlying cancer will also improve the paraneoplastic syndrome. Ideal treatment is to excise the tumor (23). A number of medications (such as ketoconazole and metyrapone) decrease cortisol synthesis (19) and can be used prior to definitive management with surgery or chemoradiotherapy.

Acromegaly

Ectopic growth hormone releasing hormone (GHRH)

secretion from malignant cells can manifest as acromegaly (24); in the case of lung cancer, bronchial carcinoids (25) and epidermoid carcinomas (26) have been implicated; SCLC have been reported less frequently (27,28). Surgical removal of the primary tumor is usually the most successful treatment option (29,30). Somatostatin analogs suppress growth hormone release and are another management option (31,32).

Pulmonary carcinoid syndrome

Bronchopulmonary neuroendocrine tumors (BP-NET) comprise approximately 20% of all lung cancers (33). Less than 5% of patients with BP-NET present with carcinoid syndrome (33). Lung NET produce less serotonin than midgut NET accounting for a lower rate of carcinoid syndrome (33). Patients with a Lung NET who have carcinoid syndrome may have atypical symptoms such as episodes of flushing which are excessively prolonged (34). The specific hormone mediator of flushing in patients is unclear in these patients. In some cases, blood serotonin or urine 5-hydroxyindoleacetic acid (5-HIAA) levels are normal. The risk of carcinoid crisis is low in these patients and prophylactic octreotide is not recommended by most clinicians prior to tumor manipulation (34).

Neurological syndromes

Paraneoplastic neurological syndromes (PNSs) are autoimmune in nature; unlike most paraneoplastic syndromes, they are independent of local tumor or metastatic effects (35). Onconeural antibodies appear to be central to the pathogenesis, though their absence does not preclude a diagnosis of PNS (36). These antibodies are directed against tumor cells but can also target the nervous system (central and peripheral), resulting in the wide-ranging manifestations of PNS.

In cases of possible or definite PNS all other possible causes of neurological causes should be excluded like brain or leptomeningeal metastasis, nerve root or spinal cord invasion or compression, electrolyte disturbances, hyperglycemia, or adverse effects to irradiation or chemotherapy.

A number of onconeural antibodies have been identified, such as Anti-Hu, Anti-CV2, anti-amphiphysin and Anti-Ri (2). Anti-Hu antibodies are the most commonly detected and 90% of Anti-Hu syndrome cases are seen in SCLC (2). The term Anti-Hu syndrome is broad, and encompasses several entities including limbic encephalitis (LE) (37), cerebellar degeneration, opsoclonus-myoclonus, neuropathies and gastric pseudo-obstruction. Some of these are discussed in detail here along with various treatment modalities.

LE

LE has is characterized by acute or sub-acute neuropsychiatric symptoms including changes in mood, memory, seizures and cognitive function (37). Symptoms typically progress over days to months. Characteristic EEG and MRI findings can support the diagnosis.

SCLC is the most commonly associated malignancy, with most patients being anti-Hu antibody positive. In addition to treatment of the malignancy, paraneoplastic LE can respond, sometimes dramatically so to immunotherapy (38).

Lambert-Eaton myasthenia syndrome (LEMS)

LEMS is a disorder of the neuromuscular junction resulting from decreased pre-synaptic acetylcholine release. Nearly half have an associated malignancy (38). The basis is autoimmune and antibodies directed against the voltage-gated calcium channel (VGCC) are usually involved in paraneoplastic LEMS. Paraneoplastic LEMS is almost invariably associated with SCLC (38); autoantibodies target the VGCCs expressed on the surface of tumor cells. This results in decreased acetylcholine release and inhibition of synaptic conduction.

The hallmark of LEMS is proximal muscle weakness, predominantly affecting the lower extremities (starting from the pelvic girdle) (39). Upper extremity involvement is usually milder and weakness can progress in a craniocaudal direction (39). Muscle weakness in the setting of SCLC in addition to characteristic electromyography (EMG) changes and the presence of autoantibodies are supportive of the diagnosis. Symptoms improve with treatment of the underlying malignancy (40). Targeted therapy for symptomatic LEMS with 3,4-diaminopyridine is usually first line; the use of guanidine with or without acetylcholinesterase inhibitors (40) is limited by marrow suppression and nephrotoxicity. Steroids, intravenous immunoglobulin (IVIg), immunosuppressants and plasma exchange are options for refractory cases (41).

Subacute cerebellar degeneration (SCD)

Paraneoplastic SCD is rare and most commonly associated with SCLC. Autoantibodies directed at the cerebellum,

particularly the Purkinje cells are involved in the pathogenesis (37). In contrast to anti-Hu associated PNSs, SCD is usually associated with anti-Yo, anti-Tr and anti-metabotropic glutamate receptor 1 (mGluR1) antibodies. Radiographic evidence of cerebellar atrophy is initially absent (37) but can develop as the disease progresses.

Symptoms of cerebellar dysfunction such as nausea, vomiting, vertigo, gait instability and ataxia are typically present. Prognosis is usually poor and immunotherapy results in modest improvement at best (37); disease progression and permanent neurologic disability is often seen.

Subacute sensory neuropathy (SSN)

Paraneoplastic SSN is a constellation of neurologic symptoms beginning with the loss of vibratory and joint sense and progressing, usually within 12 weeks, to impaired temperature sensation and pain. The pain is described as shock-like and ataxia is common. Symptoms can involve all 4 extremities, often asymmetrically (37). SCLC is the most commonly associated malignancy. Electrophysiology demonstrates significant sensory fiber disturbance, minimal motor nerve involvement, depressed or absent tendon reflex and often autonomic, cerebellar, or cerebral abnormalities (37).

Prompt recognition and treatment of the malignancy offers the best chance of improvement in neurologic symptoms (35). Compared with other PNSs, response to glucocorticoids, IVIg, plasma exchange and immunosuppressants is poor, though there is some evidence that combination treatments may result in better outcomes (41).

Glomerular diseases

In 1966, Lee *et al.* (42) reported an increased incidence of nephrotic syndrome in patients with malignancies. Since then, several cases of paraneoplastic glomerulopathy have been reported. Lung cancer is usually associated with paraneoplastic nephrotic syndromes, the most common of which is membranous glomerulopathy (MGN) (43). However, cases of minimal change disease (MCD), IgA Nephropathy, Membranoproliferative glomerulonephritis (MPGN), Focal segmental glomerulosclerosis among others have also been reported.

Nephrotic syndrome usually manifests either before or at the time of cancer diagnosis; less frequently, it occurs after the diagnosis (44). The pathogenesis might involve host-antibody response to tumor antigen shedding (45); these complexes might suppress the antineoplastic effects of cytotoxic lymphocytes (46). The detection of these antibodies or complexes is usually not necessary for the diagnosis; excluding alternate etiologies and improvement in the nephrotic syndrome associated with treatment of the malignancy can point towards the diagnosis.

Surgical resection of the primary tumor has been shown in some cases to resolve paraneoplastic nephrotic syndrome (47,48). In the case of advanced disease or unresectable lung cancer, treatment is less clear. Chemotherapy and radiotherapy have also been used successfully, for both SCLC and advanced NSCLC (48); tumor progression, however, lead to the recurrence of renal disease (48). Carboplatin based regimens are preferentially used, given the nephrotoxicity of cisplatin.

MCD is a smaller proportion of paraneoplastic glomerulopathy; though usually seen in conjunction with Hodgkin's Lymphoma, cases with lung cancer have also been reported. Treatment of the primary tumor and early use of steroids are the cornerstones of the management of paraneoplastic MCD.

Hematologic syndromes

Hypercoagulability

Venous thromboembolism (VTE)

VTE including DVT, PE and superficial vein thrombosis occurs in nearly 3% of lung cancer patients within the first 2 years of diagnosis (49). Patients with lung cancer have a 20-fold increase in risk of VTE compared to the general population (49). NSCLC confers a higher VTE risk than SCLC, and adenocarcinomas are associated with a higher risk of VTE than squamous cell carcinoma (3,50). Distant metastases confer a fold increase in VTE compared to localized tumors (51). More so, tissue factor (TF), which initiates the coagulation cascade and cancer procoagulant have an increased expression in lung cancer cells (52). TF-bearing microparticles, possibly originating from malignant cells themselves, may also contribute to a prothrombotic state.

Treatment of cancer-associated venous thromboembolic disease depends on a number of factors, including medical comorbidities (renal, hepatic disease), drug interactions, bleeding risk and reversibility, setting (inpatient/outpatient), compliance and cost. The NCCN (National Comprehensive Cancer Network) has developed guidelines (year 2018) to guide clinical decision-making. Single-agent LMWH is the preferred therapeutic anticoagulation option for cancer-related VTE (NCCN) (53) Randomized

trials have shown LMWH to have an equal or decreased risk of VTE compared with LMWH plus VKA (vitamin K antagonist) combination regimens (53). More so, the risk of major bleeding and survival rates are comparable between the mono and combination therapy groups. LMWH has consistently been shown to be superior to VKA in the prevention of recurrent cancer-related VTE (53). Trials for LMWH and VKA did not compare the 2 for a duration longer than 6 months. Among the LMWHs, the efficacy of dalteparin is supported by the highest-quality evidence for cancer-related VTE (53). LMWHs must be used cautiously in patients with renal dysfunction.

Among the DOACs (direct-acting oral anticogaulants), rivaroxaban was shown to have similar or better efficacy than dalteparin, with a slightly increased bleeding risk and equal survival rates at 6 months (53,54). Combination treatment with initial LMWH followed by longer-term edoxaban is an alternate regimen, though the risk of bleeding was significantly higher in the combination regimen (Hokusai-VTE Cancer). Randomized trials comparing apixaban with LMWH for the treatment of cancer-related VTE are underway. DOACs are contraindicated in patients with Stage IV chronic kidney disease and active or clinically significant liver disease. DOACs have been associated with increased bleeding risk in patients with gastrointestinal or genitourinary lesions, surgery or instrumentation and therefore must be used cautiously in these groups (51,54).

Recently, results from the CASSINI Trial, showed that primary prophylaxis with rivaroxaban reduced the risk of VTE and VTE-related deaths in high-risk cancer patients (55). Apixaban was also shown to be beneficial in reducing risk of VTE in intermediate to high-risk cancer patients. Both studies did result in more bleeding episodes in the anticoagulation group as compared to placebo.

Trousseau's syndrome

'Trousseau's syndrome' originally described migratory thrombophlebitis occurring in association with malignancy, but the term has also been used in reference to cancer-related hypercoagulability syndromes (56). The pathogenesis is complex, but possibly involves factor X-mediated intravascular coagulation, as observed in studies involving adenocarcinomas (57). LMWH is typically used to manage the various manifestations of Trousseau's syndrome (58). Warfarin does not appear to be as effective, possibly because it does not target selectin-binding (unlike heparin), which might a central process in the pathogenesis (59). There is no evidence for the role of anti-platelet agents.

Rheumatologic syndromes

Hypertrophic pulmonary osteoarthropathy (HPO)

HPO is the proliferation of distal cutaneous and osseous tissues (60,61) resulting in clubbing of the fingers and toes, symmetric painful arthropathy and long bone periostosis. HPO is most frequently associated with lung cancer (62,63). Unlike rheumatoid arthritis, there are no erosions or inflammatory synovitis, and there is no joint space narrowing as seen in osteoarthritis (64). Bone scintigraphy can show periosteal thickening, typically in the tibiae and fibulae (62,63). The pathophysiology of HPO is poorly understood, but it may involve overexpression of vascular endothelial growth factor (VEGF) (65) and PDGF.

Treatment of the primary malignancy has been shown to resolve HPO (62). Targeted therapy for gefitinib has also been used (66). Additionally, there have been reports of bisphosphonates, particularly pamidronate with potential anti-VEGF properties (67), and octreotide providing significant symptomatic relief (68).

Inflammatory myopathies

Polymyositis (PM) and dermatomyositis (DM) are autoimmune inflammatory myopathies sometimes seen in the setting of malignancy. They are characterized by proximal, painless muscle weakness; dermatomyositis is associated with a heliotrope rash (purple periorbital discoloration), Gottron papules (purple papules and plaques on the dorsum of both hands) and less frequently photosensitivity (69) (*Figure 1*).

DM is associated with malignancy in 10–40% of cases and often arises within 1 year of cancer diagnosis (70,71). While more commonly seen with nasopharyngeal, breast and ovarian cancers, an association with lung cancer has been observed (72,73). SCLC is more commonly associated with DM than squamous cell carcinoma (74).

High-dose oral glucocorticoid therapy is the first-line medical treatment for inflammatory myopathies and should be considered in addition to addressing the underlying malignancy (74,75). Methotrexate/azathioprine or rituximab can be considered for refractory disease.

Paraneoplastic dermatologic syndromes

Acanthosis nigricans (AN)

AN is the thickening and hyperpigmentation of the skin

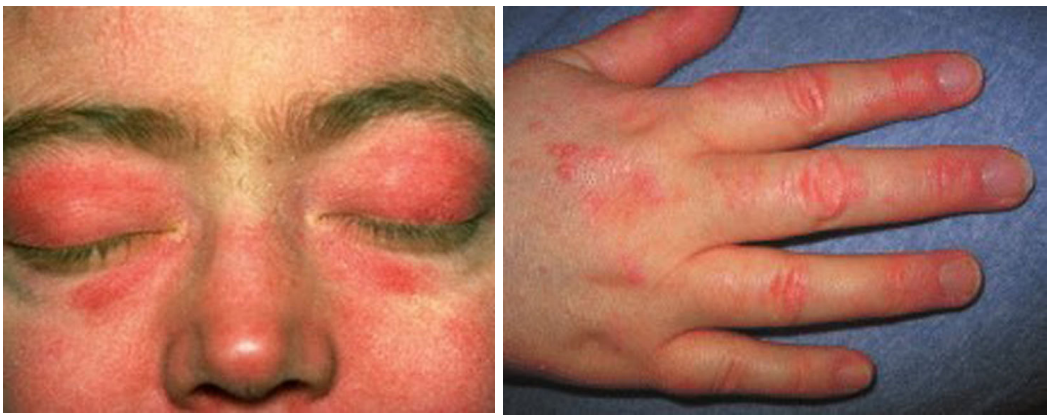

Figure 1 Heliotrope rash on the left and Gottron papules on the right. Evaluation includes autoantibody testing (including ANA, Anti-Jo-1) and evidence of myositis (elevated CK and aldolase). The inflammatory myopathies have characteristic EMG findings which support the diagnosis. Definitive diagnosis is with muscle biopsy. EMG, electromyography.

in intertriginous regions (neck folds, axilla) (3). Oral lesions are less common. Although AN is associated with endocrinopathies, a paraneoplastic variant is also seen (3). Paraneoplastic AN is commonly associated with intra-abdominal tumors and less commonly with NSCLC (76,77). Some patients develop concurrent 'tripe palms,' with velvety, rugose thickening of the palms and less commonly the soles which are also associated with malignancy (78). In some cases, tripe palms are the presenting feature of an underlying malignancy. Abnormalities in insulin-like growth factor (IGFR) receptors and fibroblasts have been observed in these cutaneous syndromes. AN and tripe palms typically improve significantly with treatment of the underlying malignancy (79) and topical retinoids are also useful.

Conclusions

This review aimed to summarize current perspectives on paraneoplastic syndromes associated with lung cancer and their management. Treating the underlying cancer is most likely to improve the effects of paraneoplastic syndromes. Greater research into their underlying mechanisms is being used to develop targeted therapies.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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