Paraneoplastic Syndromes

STAAB SYMPOSIUM

OKLAHOMA CANCER SPECIALISTS AND RESEARCH INSTITUTE

SCOTT COLE MD

Paraneoplastic Syndromes

- Describe the etiologies of the most commonly seen paraneoplastic syndromes
- Describe the etiologies of the paraneoplastic syndromes
- Explain how to evaluate a patient for a paraneoplastic syndrome
- Summarize the importance of interprofessional teams in improving care coordination and outcomes for patients with paraneoplastic syndromes
- Review the treatment options available for paraneoplastic syndromes

Paraneoplastic Syndromes

A diverse group of disorders which are not directly attributable to tumor invasion, tumor compression or metastasis. They are attributed to tumor secretion of functional peptides and hormones (ie endocrine paraneoplastic syndromes) or immune cross-reactivity between tumor and normal host tissues (ie neurologic paraneoplastic syndromes).

Paraneoplastic syndromes may affect diverse organ systems, most notably the endocrine, neurologic, dermatologic, rheumatologic, and hematologic systems.

The most commonly associated malignancies include small cell lung cancer, breast cancer, gynecologic tumors, and hematologic malignancies.

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Paraneoplastic Syndromes

Because paraneoplastic syndromes often cause considerable morbidity, effective treatment can improve patient quality of life, enhance the delivery of cancer therapy, and prolong survival.

Treatments include addressing the underlying malignancy, immunosuppression (for neurologic, dermatologic, and rheumatologic paraneoplastic syndromes), and correction of electrolyte and hormonal derangements (for endocrine paraneoplastic syndromes).

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Paraneoplastic Syndromes

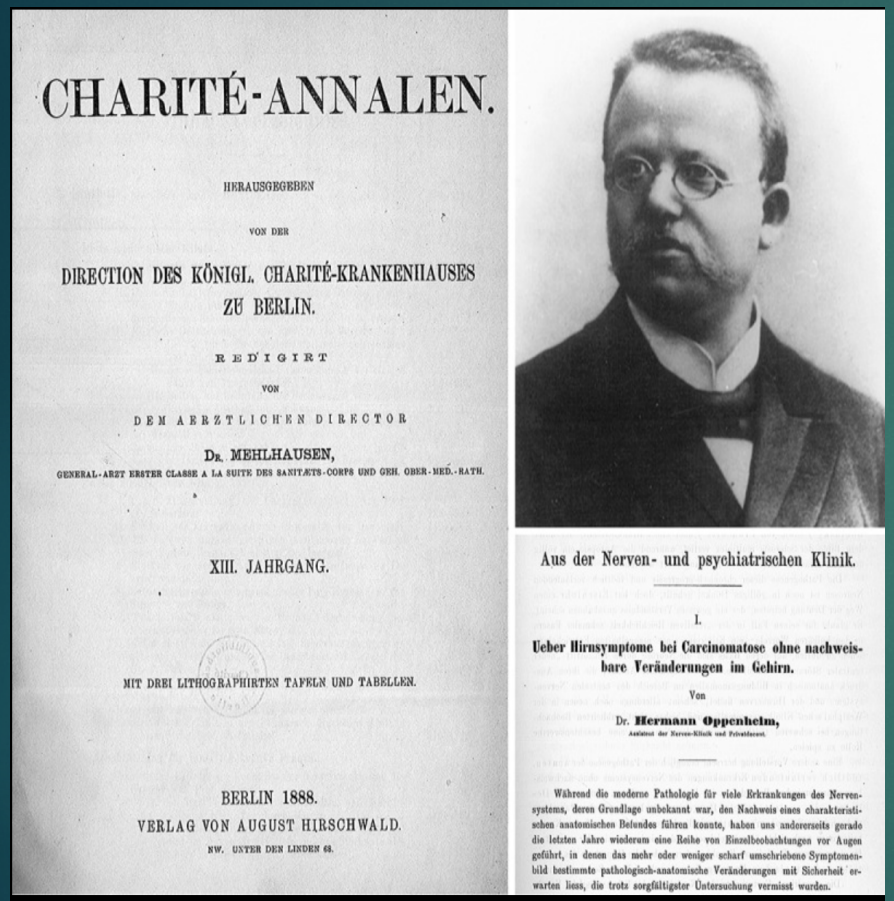
It is estimated that paraneoplastic syndromes affect up to 8% of patients with cancer

Oklahoma has roughly 20,540 new cancer cases a year (NCI)

3417 new cancer diagnoses in Tulsa County (roughly 273 new PNS cases per year)

Cristina Sardiña González, Clara Martínez Vivero, José López Castro, Paraneoplastic syndromes review: The great forgotten ones, Critical Reviews in Oncology/Hematology, Volume 174, 2022, 103676,

History


CHARITÉ-ANNALEN.

HERAUSGEGEBEN

VON DER

DIRECTION DES KÖNIGL. CHARITÉ-KRANKENHAUSES

ZU BERLIN.

REDIGIRT

VON

DEM AERZTLICHEN DIRECTOR

DR. MEHLHAUSEN,

GENERAL-ARZT ERSTER CLASSE A LA SUITE DES SANITÄTS-CORPS UND GEH. OBER-MED.-RATH.

XIII. JAHRGANG.

MIT DREI LITHOGRAPHIRTEN TAFELN UND TABELLEN.

BERLIN 1888.

VERLAG VON AUGUST HIRSCHWALD.

NW. UNTER DEN LINDEN 68.

Aus der Nerven- und psychiatrischen Klinik.

I.

Ueber Hirnsymptome bei Carcinomatose ohne nachweisbare Veränderungen im Gehirn.

Von

Dr. **Hermann Oppenheim,**

Assistent der Nerven-Klinik und Privatdocent.

Während die moderne Pathologie für viele Erkrankungen des Nervensystems, deren Grundlage unbekannt war, den Nachweis eines charakteristischen anatomischen Befundes führen konnte, haben uns andererseits gerade die letzten Jahre wiederum eine Reihe von Einzelbeobachtungen vor Augen geführt, in denen das mehr oder weniger scharf umschriebene Symptomenbild bestimmte pathologisch-anatomische Veränderungen mit Sicherheit erwarten liess, die trotz sorgfältigster Untersuchung vermisst wurden.

Figure 1. Hermann Oppenheim, the famous neurologist of the late-nineteenth and early-twentieth centuries, published his remarkable case "On Brain Symptoms Associated with Carcinomatosis without Detectable Changes in the Brain" in the 1888 issue of the *Charité Annalen*, at that time a renowned annual collection of clinical cases and observations at the Charité Hospital in Berlin.

- Hermann Oppenheim (1858–1919)
- In 1888, He reported an empiric association of peripheral neuropathy and lung cancer highlighting the remote or indirect effect of cancer on the nervous system.
- In 1890 he diagnosed the first brain tumor to be removed in Germany by Koehler, and he fostered the development of neurosurgery
- Conducted the first comprehensive music assessment as part of a neurologic examination and presented the first case series of music in aphasia.
- Oppenheim's sign: He drew attention to the association of spasticity with hyper-reflexia: "Stiffness, rigidity, or spastic condition of the muscles can be recognized from exaggeration of the tendon phenomenon." ie a Babiniski's sign
- If the irritation is made strongly enough, distinct plantar flexion of the toes is the rule, but sometimes it is necessary to divert the attention of the patient to obviate voluntary movements. Whereas in persons with the symptom complex of spastic hemiparesis, this reflex movement of the muscles is extended to the great toe and adducts or abducts the foot." https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1738441/pdf/v074p00569.pdf
- Ulitmately wasn't rewarded a Chair in his department, because of the official governmental anti-Semitism, which overruled the university's nomination of Oppenheim as Professor Extraordinarius.

H. Uber hirnsymptome gei carcinomatose ohne nachweibare veranderungen um gehirm. Charite-Ann Berlin. 1888;13:335–344.r patients in 1890

Paraneoplastic Syndrome

What are the different types of Paraneoplastic Syndrome?

Paraneoplastic Syndrome

What are the different types of Paraneoplastic Syndrome?

- Endocrine
- Rheumatologic
- Hematologic
- Neurologic

Paraneoplastic Endocrine Syndromes

- Tumor production of hormones or peptides that lead to metabolic derangements.
- Usually detected in patients after a cancer diagnosis has been made
- Treatment of the underlying tumor often improves these conditions.
- Development of these disorders does not often necessarily correlate with the cancer stage or prognosis and may even occur before the diagnosis of cancer is made.
- must be clinical or biochemical evidence of an endocrine abnormality in a patient with neoplastic disease, without any concomitant native endocrine organ dysfunction that might explain the syndrome as well

Ahmadieh H, Arabi A. Endocrine paraneoplastic syndromes: a review. Endocrinol Metab Int J. 2015;1(1):15-25

Paraneoplastic Endocrine Syndromes

- Hypercalcemia of malignancy
  - 10% of patients with cancer (Lung, breast head and neck, renal cell, ovarian)
  - 80% ectopic PTHrP (usually squamous cells): usually low PTH and nml 1,25-(OH) 2D, 20% osteolysis (breast, myeloma, lymphoma), <5 % excessive 1,25 dihydroxyvitamin D, < 1% ectopic PTH production
  - Treat the underyling tumor along with volume resuscitation, bisphosphonates/denosumab, glucocorticoids and calcitonin
- Ectopic Cushing Syndrome
  - 5-10% of cases of Cushing's syndromes are paraneoplastic
  - Presentation typically precedes a cancer diagnosis
  - Small cell lung cancers, medullary thyroid cancers, bronchial carcinoids and neuroendocrine carcinoma
  - Tumor secretion of ACTH or coricotropin-releasing factor resulting in release of cortisol
  - Failure to respond to high dose dexamethasone test distinguishes ectopic ACTH production from pituitary
  - Treat the underlying tumor and inhibit steroid production

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Paraneoplastic Endocrine Syndromes

- SIADH
  - 1-2% of all patients with cancer (10-45% of small cell cancer patients have SIADH)
  - Treat the underlying tumor and fluid restriction < 1L
- Hypoglycemia
  - Quite rare and caused by insulin-producing islet-cell tumors and extrapancreatic tumors (ie non-islet cell tumor hypoglycemia)
  - Characterized by hypoglycemia with glucose levels as low as 20
  - Treat the underyling tumor and maintain adequate blood glucose levels

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Syndrome	Clinical presentation	Laboratory findings	Associated cancers	Treatment options[c]	References
SIADH	Gait disturbances, falls, headache, nausea, fatigue, muscle cramps, anorexia, confusion, lethargy, seizures, respiratory depression, coma	Hyponatremia: mild, sodium 130-134 mEq/L; moderate, sodium, 125-129 mEq/L; severe, sodium <125 mEq/L Increased urine osmolality (>100 mOsm/kg in the context of euvolemic hyponatremia)	Small cell lung cancer, mesothelioma, bladder, ureteral, endometrial, prostate, oropharyngeal, thymoma, lymphoma, Ewing sarcoma, brain, GI, breast, adrenal	Restrict fluids (usually <1000 mL/d) and encourage adequate salt and protein intake Demeclocycline, 300-600 mg orally twice daily Conivaptan, 20-40 mg/d IV Tolvaptan, ~10-60 mg/d orally Hypertonic (3%) saline at <1-2 mL/kg/h	5-7
Hyper-calcemia	Altered mental status, weakness, ataxia, lethargy, hypertonia, renal failure, nausea/vomiting, hypertension, bradycardia	Hypercalcemia: mild, calcium 10.5-11.9 mg/dL; moderate, calcium 12.0-13.9 mg/dL; severe, calcium ≥14.0 mg/dL Low to normal (<20 pg/mL) PTH level Elevated PTHrP level	Breast, multiple myeloma, renal cell, squamous cell cancers (especially lung), lymphoma (including HTLV-associated lymphoma), ovarian, endometrial	Normal saline, 200-500 mL/h Furosemide, 20-40 mg IV (use with caution and only after adequate fluid resuscitation) Pamidronate, 60-90 mg IV Zoledronate, 4 mg IV Prednisone, 40-100 mg/d orally (for lymphoma, myeloma) Calcitonin, 4-8 IU/kg SC or IM every 12 h Mithramycin, 25 μg/kg IV (often requires multiple doses) Gallium nitrate, 100-200 mg/m^2/d IV continuous infusion for 5 d Hemodialysis	4, 8, 9
Cushing syndrome	Muscle weakness, peripheral edema, hypertension, weight gain, centripetal fat distribution	Hypokalemia (usually <3.0 mmol/L), elevated baseline serum cortisol (>29.0 μg/dL), normal to elevated midnight serum ACTH (>100 ng/L) not suppressed with dexamethasone	Small cell lung cancer, bronchial carcinoid (neuroendocrine lung tumors account for ~50%-60% of cases of paraneoplastic Cushing syndrome), thymoma, medullary thyroid cancer, GI, pancreatic, adrenal, ovarian	Ketoconazole, 600-1200 mg/d orally Octreotide, 600-1500 μg/d SC or octreotide LAR, 20-30 mg IM monthly Aminoglutethimide, 0.5-2 g/d orally Metyrapone, ~1.0 g/d orally Mitotane, 0.5-8 g/d orally Etomidate, 0.3 mg/kg/h IV Mifepristone, 10-20 mg/kg/d orally Adrenalectomy	10-14
Hypo-glycemia	Sweating, anxiety, tremors, palpitations, hunger, weakness, seizures, confusion, coma	For non–islet cell tumor hypoglycemia: low glucose, low insulin (often <1.44-3.60 μIU/mL), low C-peptide (often <0.3 ng/mL), elevated IGF-2:IGF-1 ratio (often >10:1) For insulinomas: low glucose, elevated insulin, elevated C-peptide, normal IGF-2:IGF-1 ratio	Mesothelioma, sarcomas, lung, GI	Glucose (oral and/or parenteral) Dexamethasone, 4 mg 2 or 3 times daily Prednisone, 10-15 mg/d Diazoxide, 3-8 mg/kg/d orally divided in 2 or 3 doses Glucagon infusion, 0.06-0.3 mg/h IV Octreotide, ~50-1500 μg/d SC or octreotide LAR, 20-30 mg IM monthly (often with corticosteroids) Human growth hormone, 2 U/d SC (often with corticosteroids)	4, 15-20

[a] ACTH = adrenocorticotropic hormone; GI = gastrointestinal; HTLV = human T-lymphotropic virus; IM = intramuscular; IV = intravenous; LAR = long-acting release; PTH = parathyroid hormone; PTHrP = PTH-related protein; SC = subcutaneous; SIADH = syndrome of inappropriate antidiuretic hormone secretion. See Glossary at end of article for expansion of additional abbreviations.

[b] SI conversion factors: To convert calcium values to mmol/L, multiply by 0.25; to convert cortisol values to nmol/L, multiply by 27.588; to convert C-peptide values to nmol/L, multiply by 0.331; to convert insulin values to pmol/L, multiply by 6.945; to convert osmolality values to mmol/kg, multiply by 1; to convert PTH values to ng/L, multiply by 1; and to convert sodium values to mmol/L, multiply by 1.

[c] In addition to treating the underlying malignancy.

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Paraneoplastic Dermatologic and Rheumatologic Syndromes

- Management of dermatologic and rheumatologic paraneoplastic syndromes consists of cancer-directed therapy plus standard treatments of the nonparaneoplastic counterparts of these syndromes
- less responsive to therapy than are the nonparaneoplastic equivalents.
- precedes a diagnosis of cancer or recurrence of a previously treated malignancy.

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Paraneoplastic Dermatologic and Rheumatologic Syndromes

- Acanthosis Nigrans
  - Characterized by thickened hyperpigmented skin usually involving the axilla and neck region caused by production of transforming growth factor of and epidermal growth factors
  - Usually occurs in persons with insulin resistance or nonmalignant endocrine disorders
  - Approximately 90% of cases involving the palms (tripe palms) have been shown to be cancer related/associated
  - Approximately half of the patient's have mucosal involvement
  - Gastric adenocarcinoma is most commonly associated malignancy
  - Treatment of the underlying malignancy is the mainstay of therapy

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Paraneoplastic Dermatologic and Rheumatologic Syndromes

- Dermatomyositis
  - Inflammatory myopathy featuring multiple skin changes before the onset of proximal muscle weakness
  - Classical skin changes are a heliotrope rash on the upper eyelids along with a erythematous rash on the face neck back chest shoulders and Gottron's papules (scaly eruption over phalangeal joints mimicking psoriasis)
  - 10-25% of cases are paraneoplastic and the most commonly associated malignancies of breast, ovarian, lung and prostate cancer
  - Elevated CPK (may be followed to monitor response), EMG studies, muscle biopsy showing mixed B/T-cell perivascular inflammatory infiltrate and per-fascicular muscle fiber atrophy
  - Treat underyling malignancy and may require substantial residual motor impairment
  - Up to one third of patients will have significant residual motor impairment

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Paraneoplastic Dermatologic and Rheumatologic Syndromes

- Hypertrophic osteoarthropathy
  - characterized by periostosis and subperiosteal new bone formation along the shaft of long bones and the phalanges ("digital clubbing"), joint swelling, and pain
  - Thought to be driven by VEGF, PDGFR, and prostaglandin E2
  - 90% of cases are paraneoplastic but can be founded pulmonary fibrosis, endocarditis, inflammatory bowel disease and Graves' disease
  - Digital clubbing is found in 10% of patients with lung tumors
  - Treatment is directed at the underlying malignancy

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Paraneoplastic Dermatologic and Rheumatologic Syndromes

- Leukocytoclastic Vasculitis
  - Usually occurs with hematologic malignancies, gastrointestinal, lung or urinary tract malignanciesUsually occurs in persons with insulin resistance or nonmalignant endocrine disorders
  - Characterized by painful, burning and pruritic palpable purpura over the lower extremities
  - Thought to be driven by circulating tumor and associated antigens leading to small vessel immune complex deposition triggering complement fixation and inflammation
  - Typically precedes a cancer diagnosis however the overwhelming majority of cases are not paraneoplastic and cancer screening is not recommended
  - Treat the underyling malignancy in addition to steroids and occasionally immune directed therapy

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Paraneoplastic Dermatologic and Rheumatologic Syndromes

- Pemphigus
  - Characterized by painful mucosal lesions and a polymorphic rash on palms soles and trunk
  - Thought to arise from antibodies directed against tumor antigens which resulted in cross-reactivity against various epidermal proteins
  - Typically seen in B-cell lymphoproliferative disorders
  - Treat the underyling malignancy in addition to steroids and occasionally immune directed therapy

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Paraneoplastic Dermatologic and Rheumatologic Syndromes

- Sweet Syndrome
  - Characterized by sudden onset painful and erythematous nodules, papules, and plaques located on the face trunk extremities which coincide with neutrophilia and fever
  - Typically coincides with cancer diagnosis/recurrence
  - Most commonly associated with acute myeloid leukemia or other hematologic malignancies
  - Treat the underlying malignancy however this rarely improves symptoms

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TABLE 3. **Paraneoplastic Dermatologic and Rheumatologic Syndromes**[a]

Syndrome	Clinical presentation	Diagnostic studies/ laboratory findings	Associated cancers	Treatment options[b]	References
Acanthosis nigricans	Velvety, hyperpigmented skin (usually on flexural regions); papillomatous changes involving mucous membranes and muco-cutaneous junctions; rugose changes on palms and dorsal surface of large joints (eg, tripe palms)	Skin biopsy: histology shows hyperkeratosis and papillomatosis	Adenocarcinoma of abdominal organs, especially gastric adenocarcinoma (~90% of malignancies in patients with acanthosis nigricans are abdominal); gynecologic	Topical corticosteroids	100,102, 103
Dermatomyositis (DM)	Heliotrope rash (violaceous, edematous rash on upper eyelids); Gottron papules (scaly papules on bony surfaces); erythematous rash on face, neck, chest, back, or shoulders (the last of which is known as *shawl sign*); rash may be photosensitive; proximal muscle weakness; swallowing difficulty; respiratory difficulty; muscle pain	Laboratory findings: elevated serum CK, AST, ALT, LDH, and aldolase; EMG: increased spontaneous activity with fibrillations, complex repetitive discharges, and positive sharp waves; Muscle biopsy: perivascular or interfascicular septal inflammation and perifascicular atrophy	Ovarian, breast, prostate, lung, colorectal, non-Hodgkin lymphoma, naso-pharyngeal	Prednisone, 80-100 mg/d orally Methylprednisolone, up to 1 g/d IV Azathioprine, up to 2.5 mg/kg/d orally Methotrexate, up to 25 mg/wk orally Cyclosporine A, 100-150 mg orally twice daily Mycophenolate mofetil, 2 g/d orally Cyclophosphamide, 0.5-1.0 g/m^2 IV IVIG, 400-1000 mg/d to total 2-3 g	100, 104-106
Erythroderma	Erythematous, exfoliating, diffuse rash (often pruritic)	Skin biopsy: histology shows dense perivascular lymphocytic infiltrate	Chronic lymphocytic leukemia, cutaneous T-cell lymphoma (including mycosis fungoides), GI (colorectal, gastric, esophageal, gallbladder), adult T-cell leukemia/ lymphoma, myeloproliferative disorders	Topical corticosteroids Narrow-band UVB phototherapy	107-111
Hypertrophic osteo-arthropathy	Subperiosteal new bone formation on phalangeal shafts ("clubbing"), synovial effusions (mainly large joints), pain, swelling along affected bones and joints	Plain radiography: periosteal reaction along long bones Nuclear bone scan: intense and symmetric uptake in long bones	Intrathoracic tumors, metastases to lung, metastases to bone, nasopharyngeal carcinoma, rhabdomyosarcoma	NSAIDs Opiate analgesics Pamidronate, 90 mg IV Zoledronate, 4 mg IV Localized radiation therapy	100, 112-114
Leukocytoclastic vasculitis	Ulceration, cyanosis, and pain over affected regions (especially digits); palpable purpura, often over lower extremities; renal impairment; peripheral neuropathy	Skin biopsy: histology shows fibrinoid necrosis, endothelial swelling, leukocytoclasis, and RBC extravasation	Leukemia/lymphoma, myelodysplastic syndromes, colon, lung, urologic, multiple myeloma, rhabdomyosarcoma	Methylprednisolone, up to 1 g/d IV Prednisone, 1.0-1.5 mg/kg/d orally Dapsone, ~25-50 mg/d orally Colchicine, ~0.5 mg orally 2 or 3 times daily Methotrexate, 5-20 mg/wk orally Azathioprine, 0.5-2.5 mg/kg/d orally IVIG, 400-1000 mg/d to total 2-3 g	100, 115-119

Mayo Clin Proc. 2010 Sep; 85(9): 838–854. doi: 10.4065/mcp.2010.0099

Syndrome	Clinical presentation	Diagnostic studies/ laboratory findings	Associated cancers	Treatment options[b]	References
Paraneoplastic pemphigus (PNP)	Severe cutaneous blisters and and erosions (predominantly on trunk, soles, palms); severe mucosal erosions, including stomatitis	Serum antibodies to epithelia (against plakin proteins and desmogleins) Skin biopsy: histology shows keratinocyte necrosis, epidermal acantholysis, and IgG and complement deposition in epidermal and basement membrane zones	Non-Hodgkin lymphoma, chronic lymphocytic leukemia, thymoma, Castleman disease, follicular dendritic cell sarcoma	Prednisone, ~60-120 mg orally daily Azathioprine, ~1.5 mg/kg/d orally Cyclophosphamide, 100-150 mg/d orally Cyclosporine A (target plasma levels 100-150 ng/L) IVIG, 400-1000 mg/d to total 2-3 g Mycophenolate mofetil, 1-2 g/d orally Plasma exchange Rituximab, 375 mg/m^2 IV per dose	100, 107, 120-125
Polymyalgia rheumatica (PMR)	Limb girdle pain and stiffness	Laboratory findings: elevated serum ESR (often not as high as in nonparaneoplastic PMR) and CRP	Leukemia/lymphoma; myelodysplastic syndromes; colon; lung; renal; prostate; breast	Prednisone, ~15 mg/d orally Methotrexate, ~10 mg/wk orally	126-128
Sweet syndrome (acute febrile neutrophilic dermatosis)	Acute onset of tender, erythematous nodules, papules, plaques, or pustules on extremities, face, or upper trunk; neutrophilia; fever; malaise	Skin biopsy: histology shows a polymorphonuclear cell dermal infiltrate	Leukemia (especially AML), non-Hodgkin lymphoma, myelodysplastic syndromes, genitourinary, breast, GI, multiple myeloma, gynecologic, testicular, melanoma	Clobetasol propionate, 0.05% topical Triamcinolone acetonide, 3-10 mg/mL intralesional injection(s) Methylprednisolone, up to 1 g/d IV Prednisone, 30-60 mg/d orally Potassium iodide, 300 mg orally 3 times daily (tablets) or 1050-1500 mg/d orally of saturated solution (Lugol solution) Colchicine, ~0.5 mg orally 3 times daily	100, 101, 129-132

[a] ALT = alanine aminotransferase; AML = acute myeloid leukemia; AST = aspartate aminotransferase; CK = creatine kinase; CRP = C-reactive protein; EMG = electromyography; ESR = erythrocyte sedimentation rate; GI = gastrointestinal; IM = intramuscular; IV= intravenous; IVIG = IV immunoglobulin; LDH = lactate dehydrogenase; NSAID = nonsteroidal anti-inflammatory drug; RBC = red blood cell; SC = subcutaneous; UV = ultraviolet.

[b] In addition to treating the underlying malignancy.

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Paraneoplastic Hematolgic Syndromes

- Rarely symptomatic
- Usually contacted after a malignant diagnosis has been confirmed
- Usually seen with advanced disease
- Rarely require specific therapy
- Improves with treatment of underlying

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Paraneoplastic Hematolgic Syndromes

- Eosinophilia
  - Caused due to tumor production of eosinophilic growth factors notably IL-2, IL-5, GM-CSF and usually asymptomatic
  - Distinguished from primary eosinophilia which is driven by a clonal phenomena caused directly by a hematologic malignancy and associated with gene rearrangements involving FGFR1, FIP1L1, PDGFR α/β
  - Patients may have elevated IL-3, IL-5, GM-CSF, IL-2 and eosinophil chemoattractant
  - Most common associated malignancies are leukemia and lymphoma but can be seen with GI, lung and gynecologic malignancies
  - Does not cause end organ damage which is usually seen with clonal eosinophilia
  - Return of eosinophilia usually indicates tumor recurrence

Mayo Clin Proc. 2010 Sep; 85(9): 838–854. doi: 10.4065/mcp.2010.0099

Paraneoplastic Hematolgic Syndromes

- Granulocytosis
  - Typically with a WBC count ranging from 12-30,000
  - Occurs in 15% of patients with solid tumors
  - Mechanism poorly understood
  - Does not require specific therapy

Mayo Clin Proc. 2010 Sep; 85(9): 838–854. doi: 10.4065/mcp.2010.0099

Paraneoplastic Hematolgic Syndromes

- Pure red cell aplasia
  - Associated with malignant thymoma but occasionally can be seen with leukemia, lymphoma and myelodysplasia
  - Need to rule out other causes including HIV, parvo B19, hepatitis, herpes virus
  - Diagnosed with a bone marrow biopsy
  - Mechanism of action in thymoma is due to ineffective eradication of auto-reactive T cells by neoplastic thymic tissue resulting in an autoimmune attack on red blood cell precursors which is in contrast to lymphoma/leukemia in which increased T cell large granular lymphocytes results in autoimmune destruction of erythrocytes
  - Treat the underlying malignancy
  - Malignant thymoma symptoms rarely resolve and may require immunosuppression and ESA therapy is not advised

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Paraneoplastic Hematolgic Syndromes

- Thrombocytosis
  - Defined as a platelet count greater than 400,000 with malignancy and occurs in approximately 35% of patients with malignancy
  - Needs to be delineated from other reactive thrombocytosis causes such as splenectomy, blood loss, iron deficiency and infection
  - Mechanism thought to occur from tumor production of cytokines such as IL-6
  - Serum IL-6 can be used to distinguish paraneoplastic/reactive causes from other clonal causes such as essential thrombocytosis, P vera, myelodysplasia and leukemia
  - JAK2 V617F mutations are not present
  - Vasomotor symptoms and thrombotic complications are not seen
  - Specific therapy is not warranted

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Syndrome	Clinical presentation	Laboratory findings	Associated cancers	Treatment options[b]	References
Eosinophilia	Dyspnea, wheezing	Hypereosinophilia (>0.5 × 10^9/L); elevated serum IL-5, IL-3, IL-2 and GM-CSF	Hodgkin lymphoma, non-Hodgkin lymphoma (B- and T-cell), chronic myeloid leukemia, acute lymphocytic leukemia, lung, thyroid, GI (pancreatic, colon, gastric, liver), renal, breast, gynecologic	Inhaled corticosteroids Prednisone, 1 mg/kg/d orally	137, 138, 141-146
Granulocytosis	Asymptomatic (no symptoms or signs of leukostasis such as neurologic deficits or dyspnea)	Granulocyte (neutrophil) count >8 × 10^9/L, typically without a shift to immature neutrophil forms; elevated LAP; elevated serum G-CSF	GI, lung, breast, gynecologic, GU, brain, Hodgkin lymphoma, sarcomas	Specific treatment not indicated	138, 147, 148
Pure red cell aplasia	Dyspnea, pallor, fatigue, syncope	Anemia (hematocrit, <20 not uncommon), low/absent reticulocytes, bone marrow with nearly absent erythroid precursors, platelet and white blood cell counts in normal ranges	Thymoma, leukemia/lymphoma, myelodysplastic syndrome	Blood transfusions Prednisone, 1 mg/kg/d orally Antithymocyte globulin, 500 mg daily IV (with corticosteroids and/or cyclophosphamide) Cyclosporine A, 100 mg orally twice daily Cyclophosphamide, 1-3 mg/kg/d orally Rituximab, 375 mg/m^2 IV per dose Alemtuzumab, 30 mg IV per dose Plasma exchange Splenectomy	149-154
Thrombocytosis	Asymptomatic (no bleeding or clotting abnormalities)	Elevated platelet count, greater than ~400 × 10^9/L; elevated serum IL-6	GI, lung, breast, gynecologic, lymphoma, renal cell, prostate, mesothelioma, glioblastoma, head and neck	Specific treatment not indicated	138, 140, 155, 156

[a] GI = gastrointestinal; GU = genitourinary; IL = interleukin; IM = intramuscular; IV = intravenous; LAP = leukocyte alkaline phosphatase. See Glossary at the end of this article for expansion of additional abbreviations.
[b] In addition to treating the underlying malignancy.

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Paraneoplastic Neurologic Syndromes

- Paraneoplastic neurologic syndromes (PNS)
  - Characterized by immune cross-reactivity between tumor cells and components of the nervous system.
  - In response to a developing cancer, a patient produces tumor-directed antibodies known as onconeural antibodies. Because of antigenic similarity, these onconeural antibodies and associated onconeural antigen-specific T lymphocytes inadvertently attack components of the nervous system as well.
  - In 80% of cases PNS are detected before cancer is diagnosed but affect less than 1% of cancer patients
  - May present with cognitive changes, ataxia, cranial nerve deficits, weakness, numbness, personality changes
    - Neuromuscular junction: Lambert-Eaton myasthenia syndrome (LEMS),
    - Peripheral Nervous System: (autonomic neuropathy and subacute sensory neuropathy)
    - Central Nervous System: (limbic encephalitis and cerebellar degeneration)
  - Onconeural antibodies often result in permanent damage and successful cancer treatment does not necessarily result in neurologic improvement.
  - Treatment is primarily immunosuppressive agents but success is variable
  - 5% of patients with small cell lung cancer and up to 10% of patients with lymphoma or myeloma develop PNS.
  - Overrepresented cancers tend to produce neuroendocrine proteins (eg, small cell lung cancer and neuroblastoma), contain neuronal components (eg, teratomas), involve immunoregulatory organs (eg, thymomas), or affect immunoglobulin production (eg, lymphoma and myeloma)

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2931619/

Paraneoplastic Syndromes: Neurologic

- Intracellular neuronal antigen – Antibodies directed against intracellular neuronal proteins are referred to as classical paraneoplastic or onconeuronal antibodies. The detection of these antibodies (table 2) almost always indicates the presence of an underlying tumor. These antibodies are surrogate markers of the paraneoplastic disorder, but in most of these disorders, the pathogenic mechanism is believed to be mediated by cytotoxic T cells.
  - Hu (type 1 antineuronal nuclear antibody [ANNA-1]),
  - Ri (also known as type 2 antineuronal nuclear antibody [ANNA-2]),
  - Yo (also known as Purkinje cell cytoplasmic antibody type 1 [PCA-1]),
  - amphiphysin, Ma2, Tr (also known as delta/notch-like epidermal growth factor-related receptor [DNER]),
  - collapsin-responsive mediator protein 5 (CRMP5)
  - recoverin.

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Paraneoplastic Syndromes: Neurologic

- Neuronal cell-surface or synaptic antigen – Antibodies directed against neuronal cell-surface or synaptic proteins which can occur with or without a malignancy. The frequency of a tumor association varies according to the antibody. They appear to have direct pathogenic effects on the target antigens. An underlying genetic predisposition may also play a role
  - antibodies against the N-methyl-D-aspartate (NMDA) receptor
  - alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor
  - gamma-aminobutyric acid type A (GABA-A) and type B (GABA-B) receptors
  - contactin-associated protein-like 2 (Caspr2), among others

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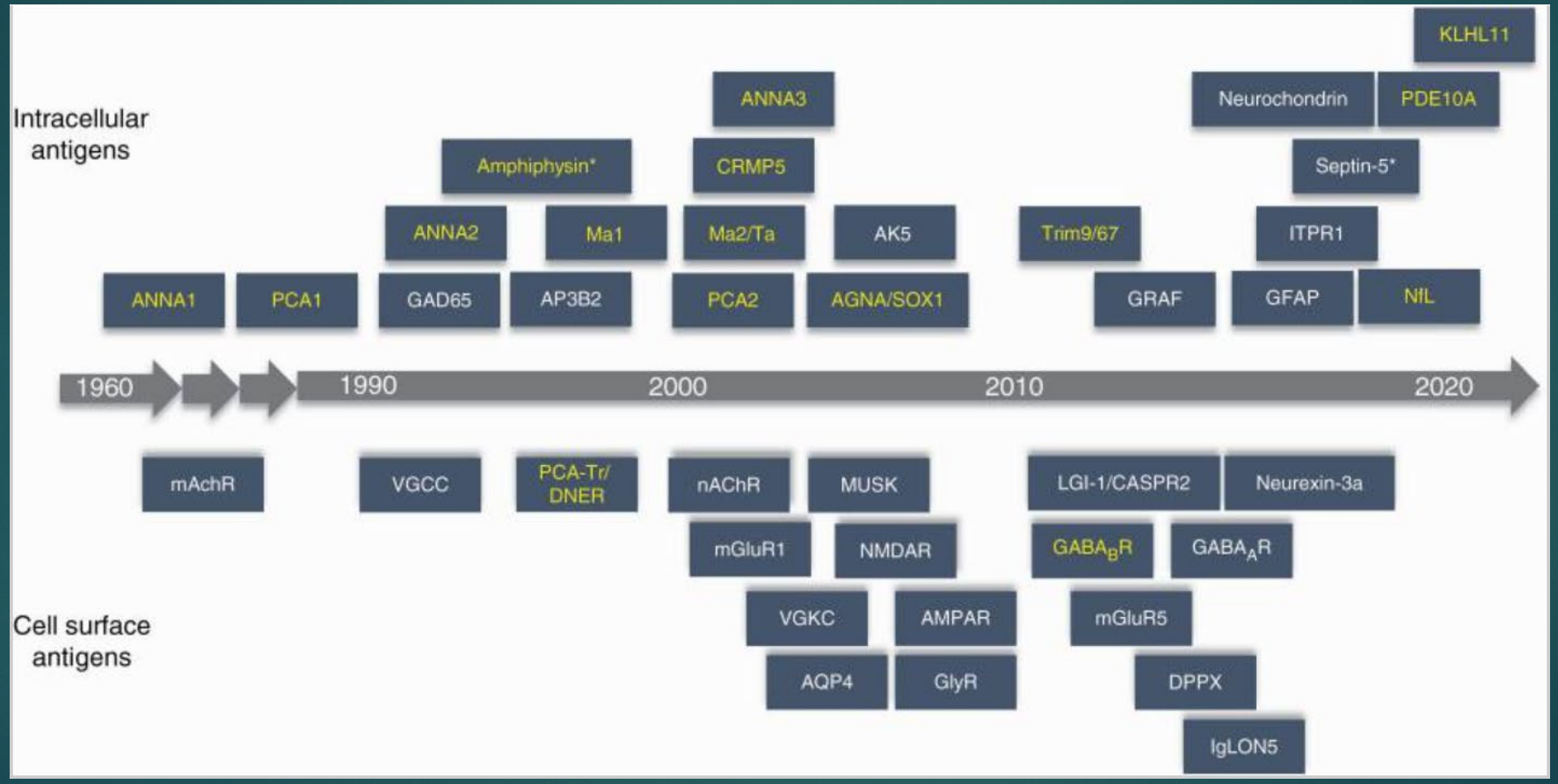
Paraneoplastic Neurologic Syndromes: Serologic Testing



Neurooncol Pract. 2021 Aug; 8(4): 362–374.

Antibodies associated with autoimmune encephalitis syndromes including paraneoplastic neurologic syndromes*

Antibody (alternative name)	Likely pathogenic mechanism	Neurologic phenotypes	Frequency of cancer (%)	Usual tumors	Sex, age-related, and other specificities
High-risk antibodies (>70% associated with cancer)					
Hu (ANNA-1)	T cell-mediated	Sensory neuronopathy, chronic gastrointestinal pseudo-obstruction, encephalomyelitis, limbic encephalitis	85	SCLC >> NSCLC, other neuroendocrine tumors, neuroblastoma	Limbic encephalitis is usually nonparaneoplastic in patients <18 years of age.
CV2/CRMP5	T cell-mediated	Encephalomyelitis, sensory neuronopathy	>80	SCLC, thymoma	Patients with an associated thymoma are younger and present more frequently with MG and less commonly with neuropathy.
SOX1	Uncertain	LEMS with and without rapidly progressive cerebellar syndrome	>90	SCLC	Stronger correlation with SCLC than with a particular neurologic presentation.
PCA-2 (MAP1B)	T cell-mediated	Sensorimotor neuropathy, rapidly progressive cerebellar syndrome, encephalomyelitis	80	SCLC, NSCLC, breast cancer	
Amphiphysin	Uncertain; possibly antibody-mediated	Polyradiculopathy, sensory neuronopathy, encephalomyelitis, stiff-person syndrome	80	SCLC, breast cancer	Associated antibodies commonly coexist. Patients with isolated antiamphiphysin are more likely to be females with breast cancer and stiff-person syndrome.
Ri (ANNA-2)	T cell-mediated	Brainstem/cerebellar syndrome, opsoclonus-myoclonus-ataxia syndrome	>70	Breast > lung (SCLC and NSCLC)	Breast cancer in females; lung cancer in males.
Yo (PCA-1)	T cell-mediated	Rapidly progressive cerebellar syndrome	>90	Ovarian cancer, breast cancer	Almost all female; in males, antigen expression by tumor should be proven.
Ma2 and/or Ma	T cell-mediated	Limbic encephalitis, diencephalitis, brainstem encephalitis	>75	Testicular cancer, NSCLC	Young males: testicular tumors and isolated Ma2 positivity; older patients: SCLC and both Ma1/2 positivity.
Tr (DNER)	Uncertain	Rapidly progressive cerebellar syndrome	90	Hodgkin lymphoma	
KLHL11	T cell-mediated	Brainstem/cerebellar syndrome	80	Testicular cancer	Young males.
Intermediate-risk antibodies (30 to 70% associated with cancer)					
AMPAR	Antibody-mediated	Limbic encephalitis	>50	SCLC, malignant thymoma	Paraneoplastic origin is more likely when other onconeuronal antibodies co-occur.
$GABA_BR$	Antibody-mediated	Limbic encephalitis	>50	SCLC	Paraneoplastic cases are more commonly observed in older males, in smokers, and in association with anti-KCTD16 antibodies. Most cases in young patients are not paraneoplastic.
mGluR5	Antibody-mediated	Encephalitis	~50	Hodgkin lymphoma	
P/Q VGCC	Antibody-mediated for LEMS; uncertain for cerebellar syndrome	LEMS, rapidly progressive cerebellar syndrome	50 (LEMS; nearly 90 for rapidly progressive cerebellar syndrome)	SCLC	Co-occurrence with N-type VGCC antibodies might be slightly more common in paraneoplastic LEMS.
NMDAR	Antibody-mediated	Anti-NMDAR encephalitis	38	Ovarian or extraovarian teratomas	Tumor (mostly ovarian teratomas) predominates in females 25 to 45 years of age (50%). Older patients less frequently have tumors (<25%), usually carcinomas. Paraneoplastic cases in children are very rare (<10%).
Caspr2	Antibody-mediated	Morvan syndrome, limbic encephalitis, acquired neuromyotonia (Isaac syndrome)	50 (for Morvan syndrome) <30 (for all other syndromes)	Malignant thymoma	Caspr2 should be considered as an intermediate-risk antibody only in the setting of Morvan syndrome. When associated with other neurologic syndromes, the risk of cancer is very low.
Lower-risk antibodies (<30% associated with cancer)					
mGluR1	Antibody-mediated	Cerebellar ataxia	30	Mostly hematologic	
$GABA_AR$	Antibody-mediated	Encephalitis	<30	Malignant thymoma	Paraneoplastic origin is less frequent in children (10%) than in adults (60%).
GFAP	Uncertain	Meningoencephalitis	~20	Ovarian teratomas, adenocarcinomas	May occur as an immunologic accompaniment in anti-NMDAR encephalitis with ovarian teratomas.
GAD65	Uncertain	Limbic encephalitis, stiff-person syndrome, cerebellar ataxia	<15	SCLC, other neuroendocrine tumors, malignant thymoma	Paraneoplastic origin more likely in older patients, males, and in association with neuronal antibodies or atypical clinical presentations.
LGI1	Antibody-mediated	Limbic encephalitis	<10	Malignant thymoma, neuroendocrine tumors	Paraneoplastic cases are mainly observed in patients with Morvan syndrome and both serum LGI1 and Caspr2 antibodies.
DPPX	Antibody-mediated	Encephalitis with CNS hyperexcitability, PERM	<10	B cell neoplasms	
GlyR	Antibody-mediated	Limbic encephalitis, PERM	<10	Malignant thymoma, Hodgkin lymphoma	
AQP4	Antibody-mediated	Neuromyelitis optica spectrum disorder	<5	Adenocarcinomas	Paraneoplastic origin associated with older age, male sex, and severe nausea/vomiting at onset.
MOG	Uncertain	MOG antibody-associated disease	5 cases reported	Mostly ovarian teratomas	
AK5	T cell-mediated	Limbic encephalitis	<1		No known cancer association
GluK2	Antibody-mediated	Encephalitis with prominent cerebellar involvement	<1		1 of 8 patients had a remote history of Hodgkin lymphoma

ANNA: antineuronal nuclear antibody; SCLC: small cell lung cancer; NSCLC: non-small cell lung cancer; CRMP5: collapsin-responsive mediator protein 5; MG: myasthenia gravis; SOX1: SRY-box transcription factor 1; LEMS: Lambert-Eaton myasthenic syndrome; PCA: Purkinje cell antibody; MAP1B: microtubule-associated protein 1B; DNER: delta/notch-like epidermal growth factor-related receptor; KLHL11: Kelch-like protein 11; AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; $GABA_BR$: gamma-aminobutyric acid-B receptor; KCTD16: potassium channel tetramerization domain containing; mGluR5: metabotropic glutamate receptor 5; P/Q VGCC: P/Q type voltage-gated calcium channel; NMDAR: N-methyl-D-aspartate receptor; Caspr2: contactin-associated protein-like 2; mGluR1: metabotropic glutamate receptor 1; $GABA_AR$: gamma-aminobutyric acid-A receptor; GFAP: glial fibrillary acidic protein; GAD: glutamic acid decarboxylase; LGI1: leucine-rich glioma inactivated protein 1; DPPX: dipeptidyl-peptidase-like protein; CNS: central nervous system; PERM: progressive encephalomyelitis with rigidity and myoclonus; GlyR: glycine receptor; AQP4: aquaporin 4; MOG: myelin oligodendrocyte glycoprotein; AK5: adenylate kinase 5; GluK2: glutamate kainate receptor subunit 2.

* Antibodies to mGluR2 and SEZ6L2 are not listed as there is an insufficient number of cases to determine risk of cancer association.

Paraneoplastic Neurologic Syndromes

- An international neurologist panel developed criteria for paraneoplastic syndrome into definite and possible categories based on the classical neurological syndrome, presence of paraneoplastic antibodies, and timing of diagnosis of the occult malignancy
  - Classical syndromes include encephalomyelitis, limbic encephalitis, subacute cerebellar degeneration, opsoclonus-myoclonus syndrome, Lambert Eaton myasthenic syndrome, subacute sensory syndrome neuropathy, chronic gastrointestinal pseudoobstruction, and dermatomyositis.
  - Definite Paraneoplastic Syndrome = a classical neurological syndrome with confirmed paraneoplastic syndrome antibodies where malignancy, if undiagnosed, is expected to be diagnosed within five years of the diagnosis of paraneoplastic syndrome.
  - Possible Paraneoplastic Syndrome = a classical neurological syndrome without paraneoplastic antibodies or cancer but at high risk for an underlying malignancy, a classical or nonclassical neurologic syndrome with partially characterized antibody but no cancer, a nonclassical syndrome without paraneoplastic antibodies but diagnosed with cancer within two years of developing the neurological syndrome.

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https://www.ncbi.nlm.nih.gov/books/NBK507890/

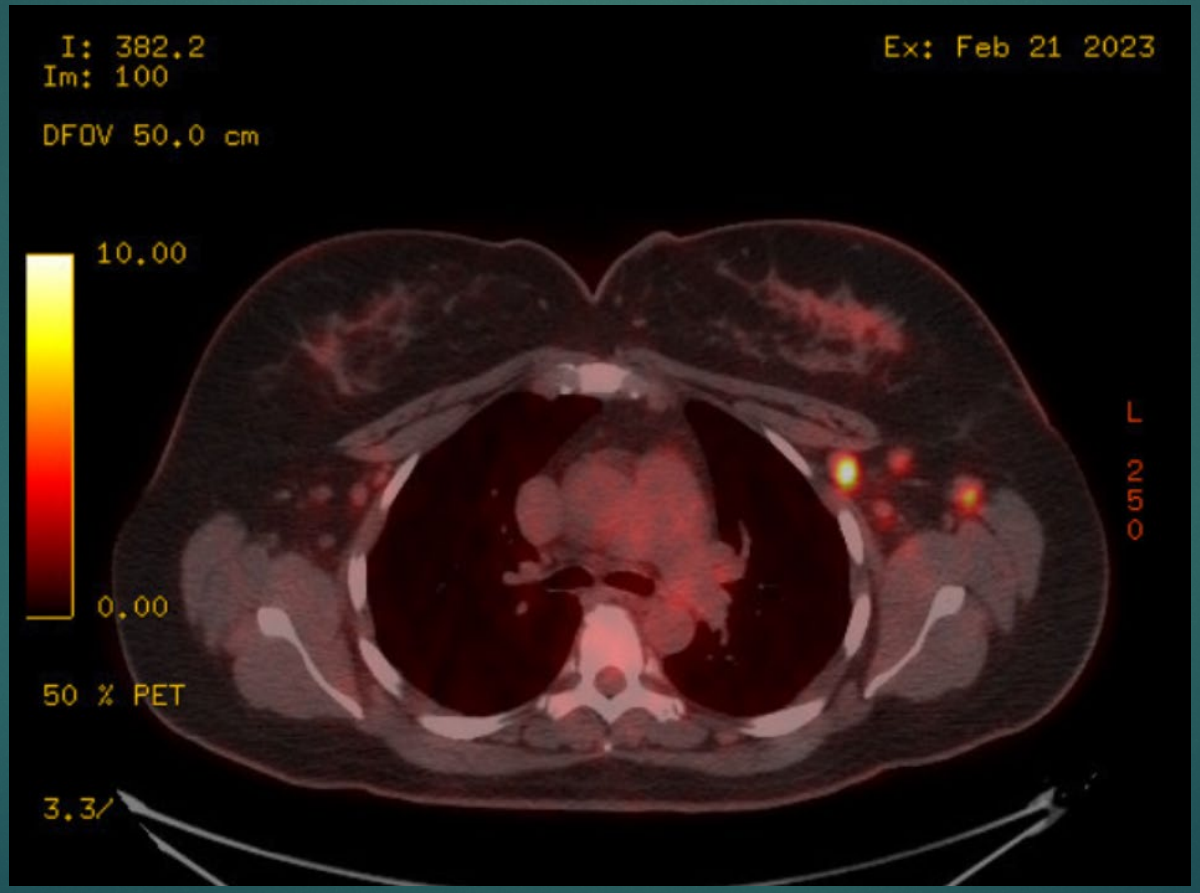
Clinical Vignette

- HPI: 47yo female found to have an abnormal screening mammogram in December of 2021 remarkable for an abnormal left axillary lymph node. No symptoms from adenopathy and no constitutional symptoms
- Past Medical History:
  - Sjogren's dx'd in 2014 with minor salivary gland biopsy and
  - Rheumatoid Arthritis treated with hydroxychloroquine
  - h/o Raynaud, not active now
  - Denies miscarriage, blood clot, hx of psoarisis, IBD
- Social History: married non smoker 1-3 alcoholic beverages per week.
- Family History: type 1 DM in father
- ROS: all normal
- Labs: CBC and CMP unremarkable
- PE: largely uremarkable, no splenomegaly, or palpable adenopathy

Clinical Vignette

- Ultrasound-guided biopsy on 1/11/2022 was remarkable for reactive follicular hyperplasia with no evidence of lymphoma
- Seen by general surgery and underwent a left axillary excisional biopsy on 11/28/2022
  - Pathology remarkable for an enlarged lymph node measuring 2.2 x 2.7 cm remarkable for no immunophenotypic evidence of lymphoma with polytypic B cells and normal flow cytometry
  - Pathology reviewed at NIH and reported on 1/3/2023 as "partial involvement by diffuse large cell lymphoma with anaplastic cytology associated with a monocytoid B-cell reaction. This is a very challenging case with extensive studies including flow cytometry and molecular studies for immunoglobulin and T-cell gene rearrangement studies failing to reveal clonal rearrangement".
  - IHC : the large atypical cells are positive for CD20(strong), OCT2, CD45, CD79a, MUM1(weak), PAX5(weak) and P53. Negative for CD30, CD15, ALK-1, CD10 BCL6, CD23, Cyclin D1, CD43, CD3, CD4, CD7, CD5 and CD8. Rare EBV positive cells are noted. Molecular studies for IG and TCR failed to reveal a clonal rearrangement for IG most likely due to relative paucity of the neoplastic cells. TCRG rearrangement was polyclonal.
  - NGS Test gene panel via True Site Oncology 500 gene panel without reportable abnormalities

Clinical Vignette



Clinical Vignette

- PET/CT imaging on 2/21/2023 remarkable for hypermetabolic bilateral cervical, axillary, retroperitoneal, bilateral iliac, and inguinal adenopathy, compatible with metabolically active lymphoma (Deauville score 4, Stage 3). No splenic or extranodal involvement
- MRI imaging of brain on 2/21/2023 unremarkable for CNS disease
- 2/6/23 PB Flow: Tiny atypical CD3 positive T-cell population of uncertain significance. No evidence of a B-cell LPD.
- Left axillary nodal dissection on 3/23/2023 remarkable for benign lymph nodes with reactive follicular hyperplasia with no diagnostic features of malignancy

Clinical Vignette

- In March 2023 pt developed night sweats and bilateral lower extremity pain and weakness.
- Outpatient MRI imaging of lower extremities in March of 2023 was unremarkable
  - Rheum panel: ANA speckled 1:320, ENA screen +, Anti-Smith -, SSB -, Anti-RNP -, SSA, Scleroderma Ab 70 -, Sjogren SSA Ro52 -, Jo-1 antibody negative, Sjorgren SSA Ro60 + at 525

Clinical Vignette

- 4/2023 Hospital admission with rhabdomyolysis
  - 4/6/23 CPK 8646 AST 364 ALT 326 TB 0.5
  - Clinical decline with proximal muscle weakness. Concern for possible paraneoplastic syndrome.
  - 4/13/23 MRI liver: 1. No liver abnormalities. No upper abdominal adenopathy. 2. Small effusions.
  - 4/13/23 MRI bilateral upper thigh: Symmetric myositis involving large muscle groups symmetrically described above without organized fluid collections
  - Tx'd with IVF's with improvement in symptoms and CPK and d/c'd to home

Clinical Vignette

- BMBx on 4/23/2023 remarkable for Mildly hypercellular marrow with mild erythroid hyperplasia and absent storage iron; No evidence of involvement by non-Hodgkin's lymphoma Peripheral blood CBC And Smear-Mild reticulocytosis without anemia
- PET/CT imaging on 4/26/2023 remarkable for a few new nonenlarged hypermetabolic retroperitoneal/left common iliac chain nodes. These are nonspecific and could be reactive or represent recurrent lymphoma.
- R-CHOP chemotherapy initiated on 5/1/2023
- She was started on 100 mg prednisone daily for 3 weeks
- Pt's pain improved but LFT's remained elevated along with new onset dysphagia with worsening proximal muscle weakness requiring a walker concerning for polymyalgia rheumatica.
  - Recommended an open muscle biopsy, EMG's studies and an evaluation at MD Anderson

Clinical Vignette

- Seen at MD Anderson in 6/2023 with Oncology, Neurology, Rheumatology, Hepatology and Neurosurgical consults.
  - EMG: consistitent with diffuse myositis, like polymyositis. No findings for neuromuscular junction dysfunction or large fiber neuropathy.
  - CT head on 6/16 was unremarkable.
  - LP 6/17, CSF neg for malignancy
  - Echo done 6/15 EF 63%
  - CSF neg for malignancy
  - MRI 6/17/23 showed heterogeneously enhancing diffuse muscle edema in right thigh representing polymyositis
  - PET 6/16/23 showed complete metabolic response, Excellent response to interval treatment with considerable decrease in size and resolution of FDG-avidity at multicompartmental lymphadenopathy.
  - Liver bx 6/26 showed atypical sinusoidal cellularity, Hepatocellular injury. No significant portal or lobular inflammation, no evidence of fatty liver disease, and no portal-based or bridging fibrosis.
  - ANA and SSA +, Neg RNP, smith, dsDNA, Jo-1, SCL 70, RF

Clinical Vignette

- Muscle biopsy on 6/20 remarkable for necrotizing myositis
  - IVIG 1g/kg for 4 days 6/19-6/22
  - Solumedrol 1000mg Q24hrs X 5 days->Prednisone taper
  - Started Tocilizumab 6/25 Q 28 days
  - Imuran given for short course but discontinued due to cytopenia.
  - Cycle 2 of RCHOP resumed on 6/26 and cycle 6 completed on 8/28/2023

Clinical Vignette

- Pt developed AMS
  - CT head showed multiple mass-like hyper-enhancement lesions in the bilateral basal ganglia, bilateral frontal lobes and bilateral midbrain
  - MRI brain multifocal homogeneously enhancing lesions throughout the brain most consistent with lymphomatous involvement, Alternatively this could represent subacute infarct.
  - PET/CT 10/10/23 Multiple FDG-avid intracranial lesions.
  - LP 10/9, FC and cytology negative.
  - Brain biopsy on 10/13/23 showed DLBCL, negative infection.
  - 3 cycles of MATRIx regimen + rituximab at MDA from 10/18/2023-11/30/2023
  - 1 cycle of LDC chemotherapy at MDA on 1/11/2024
  - Liso-Cel infusion at MDA on 1/16/2024 (no CRS or ICANS)

Thank you

- Names of medical oncologists at OCSRI