

# Paraneoplastic Syndromes

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**Author:** ScholarRx

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## Learning Objectives (4)

*After completing this brick, you will be able to:*

- 1 Describe the main paraneoplastic syndromes affecting the skin and musculoskeletal system.
- 2 Describe the main paraneoplastic syndromes affecting the endocrine system.
- 3 Describe the main paraneoplastic syndromes affecting the central and peripheral nervous systems.
- 4 Define paraneoplastic syndromes, and explain how they are different from the direct, local effects of a tumor.

Usually the signs and symptoms—things like peripheral neuropathy or delusions or kidney stones—would not immediately make you think “cancer.” But they result from some action on the part of the tumor cells, such as secretion of hormone-like substances or stimulation of an aberrant immune response.

Paraneoplastic syndromes are estimated to occur in up to 20% of patients with cancer. Some paraneoplastic syndromes are characteristic of a specific type of cancer, while others can occur in several different types of cancer. As you might expect, paraneoplastic syndromes can cause a wide variety of symptoms in just about every organ and organ system in the body. Some of the most commonly affected organs and organ systems are the nervous system, endocrine system, skin, and musculoskeletal system. In this brick, we'll focus on the most common and most notable paraneoplastic syndromes in each of these categories.

## Paraneoplastic Syndromes That Affect the Nervous System

Paraneoplastic syndromes affecting the nervous system almost exclusively result from immune responses to malignancy (ie, immunologic cross-reactivity between components of the nervous system and tumor cells). Paraneoplastic neurologic syndromes are often detected before an actual cancer diagnosis. Therefore, identifying a neurologic paraneoplastic syndrome is often the first clue to an underlying malignancy.

Two common and important paraneoplastic syndromes that affect the nervous system are covered in detail in other bricks, but they deserve brief mention here. They are myasthenia gravis and Lambert-Eaton myasthenic syndrome (LEMS). Myasthenia gravis affects postsynaptic acetylcholine

receptors and is characterized by muscle weakness that worsens as the affected muscle is used. When it occurs as a paraneoplastic syndrome, the most common underlying tumor is thymoma. LEMS affects presynaptic calcium channels and causes muscle weakness that improves as the muscle is used. It is most commonly associated with small cell lung cancer (SCLC).

### Anti-NMDA Receptor Encephalitis

Anti-NMDA receptor encephalitis (ANRE) is brain inflammation (encephalitis) due to autoantibodies to NMDA (*N*-methyl-D-aspartate) receptors in the brain, resulting in a characteristic neuropsychiatric syndrome. The tumor most commonly associated with ANRE is ovarian teratoma.

The signs and symptoms of ANRE are highly characteristic. Patients will often first have headaches, fever, or flu-like symptoms, followed by a predictable and progressive set of neuropsychiatric symptoms that begin a few days later:

- The first phase is dominated by psychiatric symptoms such as anxiety, agitation, paranoia, delusions, hallucinations, mania, unstable mood, cognitive deterioration, abnormal speech, and insomnia, along with behavior and personality changes. Seizures are most common during this phase.
- The second phase follows the first by about a week and is characterized by decreased consciousness, catatonia, and other neurologic symptoms. These include abnormal movements of the face and extremities as well as autonomic instability, seen as tachycardia or bradycardia, hypotension or hypertension, hypoventilation, and hyperthermia. Seizures and insomnia are seen in this stage as well.

ANRE itself can be lethal if not treated. Immediate treatment includes

~~Limbic encephalitis can be fatal if not treated. Immediate treatment includes steroids, intravenous immunoglobulins (IVIG), plasmapheresis, and supportive measures.~~ The offending tumor should be resected as soon as possible. Even with appropriate treatment, cognitive deficits, sleep disturbances, and behavioral abnormalities can persist for years.

What tumor is most commonly associated with anti-NMDA receptor encephalitis?

## Limbic Encephalitis

Limbic encephalitis is an immune-mediated paraneoplastic syndrome that is characterized by inflammation of the structures that compose the limbic system. The typical presentation involves subacute onset of symptoms classically associated with the limbic system. These include short-term memory loss (a hallmark symptom), seizures, personality changes, olfactory and gustatory hallucinations, headaches, agitation, and sleep disturbance.

### CLINICAL CORRELATION

Recall that the hippocampus, amygdala, cingulate gyrus, and mammillary bodies are components of the limbic system. The limbic system is responsible for the famous five Fs: feeding, fleeing, fighting, feeling, and sex.

The cancer most commonly associated with limbic encephalitis is SCLC. The underlying mechanism involves an autoimmune attack targeted at neurons in the limbic system. Antibodies against a neuronal antigen called Hu (anti-Hu antibodies) play an important role in this mechanism. While treatment of the underlying cancer is of primary importance, if symptoms are particularly troublesome, immunosuppressive treatment may provide some relief.

Which cancer is most commonly associated with limbic encephalitis?

## Paraneoplastic Syndromes That Affect the Endocrine System

Tumors sometimes do strange things for reasons that aren't entirely clear. One of these strange activities is hormone secretion (by tumors that have no business making hormones). We're not talking about a thyroid cancer secreting thyroid hormones. That makes sense. But a squamous cell lung cancer that makes parathyroid hormone? That's just strange. To be fair, these "hormones" are often not structurally identical to their normal counterparts (so we often call them hormone-like substances). But they're similar enough to the normal hormones that the body reacts to them as if they were real hormones, and patients end up with all kinds of hormone-related symptoms, sometimes well before the cancer itself makes an appearance.

It's important to note that in these hormone-related paraneoplastic syndromes, the tumor cells are just sitting there making hormone on their own, and they don't respond to any outside signals telling them to stop. This type of secretion is called ectopic, meaning that it's outside of the normal axis of hormonal control.

Normal hormone secretion is responsive to inhibiting signals. When the serum calcium level is low, the parathyroids release parathyroid hormone (PTH); when the serum calcium level reaches normal levels, PTH is no longer released. Ectopic hormone secretion is unresponsive to inhibiting signals. When a tumor cell secretes a PTH-like substance, it doesn't care about the serum calcium level! The serum calcium can be markedly elevated, and the tumor cell will keep on secreting its PTH-like substance.

There are many paraneoplastic syndromes involving the endocrine system.

Here, we'll touch on Cushing syndrome, but because of its importance and breadth, it will be covered in more depth in another brick. Then we'll focus on two of the more common syndromes: hypercalcemia and syndrome of inappropriate antidiuretic hormone secretion (SIADH). Once you understand how these syndromes work, you can apply that knowledge to any of the other hormone-related paraneoplastic syndromes you may encounter.

### Cushing Syndrome

Cushing syndrome is a common disorder caused by high levels of serum cortisol. Patients develop characteristic signs and symptoms such as deposition of adipose tissue in the upper back and neck region ("buffalo hump") and around the face ("moon facies") along with a number of metabolic derangements, including hyperglycemia.

Although there are other, more common, causes of Cushing syndrome, a small but significant number of cases are caused by a paraneoplastic syndrome. The most common culprit is SCLC, which can secrete a substance so similar to adrenocorticotrophic hormone (ACTH) that it acts just like ACTH and stimulates the production of cortisol by the adrenal gland.

### Hypercalcemia

There are many causes of hypercalcemia (serum calcium >10.2 mg/dL). When a patient is found to have hypercalcemia on a routine laboratory assay but has no clinical signs or symptoms of hypercalcemia, the most common cause is a primary hyperparathyroidism (something in the parathyroid gland itself is causing excess PTH secretion). When patients with hypercalcemia are symptomatic however that's a different story. the

With hypercalcemia are symptomatic, however, that's a different story, the most common cause of symptomatic hypercalcemia is malignancy.

Hypercalcemia is one of the most common paraneoplastic syndromes. Most malignant tumors that cause hypercalcemia do so by secreting a substance called parathyroid hormone-related protein (PTHrP), which, like normal PTH, causes the serum calcium level to increase. A number of cancers are highly associated with the production of PTHrP: most commonly squamous cell carcinoma of the lung and head and neck as well as carcinomas of the breast, ovaries, bladder, and kidneys.

Malignant tumors can also cause hypercalcemia by secreting calcitriol (the active form of vitamin D), which raises serum calcium by several different mechanisms. This is a much less common mechanism of paraneoplastic hypercalcemia, and it's seen primarily in patients with lymphoma.

What cancers are associated with paraneoplastic hypercalcemia?

#### CLINICAL CORRELATION

Recall that parathyroid hormone ultimately increases serum calcium levels and lowers serum phosphate levels. Vitamin D3 (calcitriol) ultimately increases both serum calcium and serum phosphate.

Recall that squamous cell carcinoma of the lung and SCLC are strongly associated with smoking.

Hypercalcemia can present with a variety of signs and symptoms, and key symptoms can be remembered by organ system.

To recall the key symptoms of hypercalcemia: stones, bones, groans, and psychiatric overtones.

Renal: kidney stones, polyuria, nocturia (urinating excessively at night, usually disturbing sleep), dehydration.

Musculoskeletal: Bone pain and muscle weakness.

Gastrointestinal (GI): constipation, GI upset, nausea, vomiting.

Neuropsychiatric: depression, confusion, lethargy, fatigue.

When hypercalcemia occurs as part of a paraneoplastic syndrome, calcium levels can increase to dangerously high levels. In these cases, managing the calcium level is the first priority: a search for the cause can be

the calcium level is the first priority, a search for the cause can be undertaken once the patient is stable.

## Syndrome of Inappropriate Antidiuretic Hormone

As its name implies, the paraneoplastic syndrome of inappropriate antidiuretic hormone (SIADH) results from increased levels of antidiuretic hormone (ADH) because of ectopic production by a tumor. SCLC is by far the most commonly associated cancer. ADH normally stimulates the reabsorption of water in the collecting ducts of kidney, and its action is tightly controlled by physiologic feedback mechanisms. In SIADH, however, the offending tumor releases ADH in an unregulated fashion. This excess ADH causes hyponatremia (decreased serum sodium, <135 mEq/L) through a dilutional effect in the serum and by increasing sodium excretion.

Watch for neurologic symptoms: decreased consciousness, malaise, weakness, seizures, headaches, and memory impairment. Laboratory studies will show hyponatremia, hypo-osmolality (<275 mOsm/kg), and urine that is less dilute than expected (>100 mOsm/kg).

What cancer is most commonly associated with paraneoplastic SIADH?

The immediate management of SIADH is centered on correcting serum sodium levels mainly through fluid restriction and pharmacologic intervention. As with all the paraneoplastic syndromes, the optimal treatment addresses the underlying tumor.

## Paraneoplastic Syndromes That Affect the Skin and Musculoskeletal System

Paraneoplastic syndromes that affect the skin often precede a diagnosis of cancer and are often the first symptoms of an underlying malignancy.

### Acanthosis Nigricans

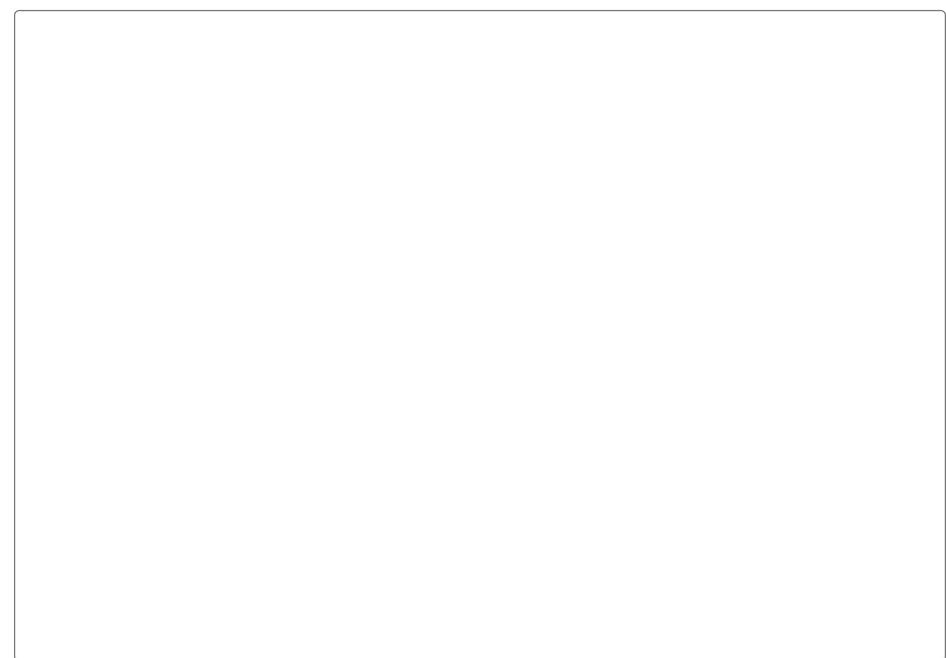
• TRUCTOR NOTE

Will be discussed further in Skin pathology sessions

MARIA PLUMMER

Acanthosis nigricans (AN) refers to thickened, black or brown hyperpigmentation of the skin that often has a velvety texture, seen here on the neck ([Figure 1](#)) and axilla ([Figure 2](#)), the most common sites. Most cases of acanthosis nigricans are associated with conditions such as

obesity or diabetes. An estimated 20% of cases, however, are related to an underlying tumor, most commonly gastric adenocarcinoma. It is thought that tumors with this type of paraneoplastic syndrome secrete growth factors that stimulate the formation of the characteristic skin lesions of acanthosis nigricans.



**QUIZ**

 Tap image for quiz

**Figure 1**



**QUIZ**

 Tap image for quiz

**Figure 2**

### Sign of Leser-Trélat

 EDITOR'S NOTE

Will be discussed further in skin pathology sessions.

MARIA PLUMMER

Leser-Trélat sign is the sudden, explosive appearance of numerous seborrheic keratoses ([Figure 3](#)). Seborrheic keratoses are gray-brown, flat-topped, velvety lesions having a “stuck-on” appearance. They are commonly seen in middle-aged and elderly patients, but they typically appear slowly over time. When they appear suddenly, and in large numbers, a search for an underlying malignancy is warranted. The most common cancers with this paraneoplastic syndrome are those involving the gastrointestinal tract. These tumors secrete a substance called transforming growth factor  $\alpha$ , which stimulates keratinocytes and may lead to the development of seborrheic keratoses.

[Figure 3](#)

## Hypertrophic Osteoarthropathy

Hypertrophic osteoarthropathy is a syndrome of digital-clubbing ([Figure 4](#)), joint swelling and synovial effusions, and joint pain (especially in the large joints). Ninety percent of cases are paraneoplastic.

[Figure 4](#)

Lung cancer (of any type) is the most commonly associated malignancy. The presence of sudden-onset digital clubbing should always prompt a work-up for an underlying malignancy. The mechanism for hypertrophic osteoarthropathy is abnormal skin proliferation and subperiosteal bone formation along the shafts of the phalanges. There is also periostosis (excessive bone formation) and periostitis (inflammation of the periosteum, the membrane that envelopes bone) of tubular bones.

## Wrapping Up

Paraneoplastic syndromes, as we've seen, are characterized by a wide range of different signs and symptoms. Their underlying mechanisms are likewise very diverse. Let's take a step back and summarize what we've covered. We discussed several different paraneoplastic syndromes, grouping them together by the organ system in which most of their symptoms occur. **Table 1** summarizes the presentation, mechanism, and most commonly associated cancers for the main paraneoplastic syndromes discussed in this brick.

**Table 1**

Syndrome	Presentation	Mechanism	Most Commonly Associated Cancers
<b>Neuromuscular</b>			
Anti-NMDA receptor	Phase 1: seizures and psychiatric disturbances. Phase 2: NMDA receptors in the brain.	Antibodies against NMDA receptors in the brain.	Ovarian teratoma

encephalitis	disturbances. Phase 2: dyskinesia, stupor, autonomic instability.	NMDA receptors in the central nervous system	Ovarian teratoma
Limbic encephalitis	Memory loss, seizure, olfactory/gustatory hallucinations, personality changes	Antibodies against Hu antigens in neurons	Small cell lung carcinoma
<b>Endocrine</b>			
Cushing syndrome	Buffalo hump, moon facies, hyperglycemia	Production of ACTH by tumor cells	Small cell lung carcinoma
Hypercalcemia	"Stones, bones, groans, and psychiatric overtones." Very high serum calcium.	Production of PTHrP or calcitriol by tumor cells	PTHRP: Squamous cell carcinomas of the lung, head, and neck; carcinomas of the breast, ovary, kidney, and bladder. Calcitriol: lymphomas.
SIADH	Decreased consciousness, memory impairment, seizures, malaise, weakness, headaches	Production of ADH by tumor cells	Small cell lung carcinoma
<b>Musculocutaneous</b>			
Acanthosis nigricans	Velvety hyperpigmentation of skin	Unclear, tumor secretion of growth factors	Gastric adenocarcinoma
Sign of Leser-Trélat	Abrupt eruptions of multiple seborrheic keratoses	Unclear, tumor secretion of growth factors	Gastrointestinal adenocarcinoma
Hypertrophic osteoarthropathy	Digital clubbing, synovial effusions, joint pain	Subperiosteal bone proliferation, periostosis of long bones	Lung cancer (all types)

## CASE CONNECTION

[BACK TO INTRODUCTION ↑](#)

Thinking back to AH, what is the diagnosis? What is the etiology of the elevated calcium level?

You suspect that AH has squamous cell carcinoma of the lung due to his tobacco use and that the hypercalcemia is due to ectopic production of PTH. You admit AH to the hospital, begin antibiotics for his pneumonia, and administer IV fluids as initial management of his hypercalcemia. “We have a few problems here,” you explain to AH. “You have pneumonia, but more seriously, you have a lung mass that I think is cancer. Your symptoms are related to an elevated calcium level that can be associated with certain lung cancers. Once the pneumonia is treated, we’ll be able to address these issues more thoroughly.”

## Summary

- Paraneoplastic syndromes are groups of signs and symptoms that happen in patients with cancer but are not directly related to the growth of the tumor itself.
- There are many such syndromes, some of which can be fatal if not treated.
- Paraneoplastic syndromes often result from immune cross-reactivity or production of hormone by the tumor cells.
- Paraneoplastic neurologic syndromes include anti-NMDA receptor encephalitis, limbic encephalitis, Lambert-Eaton myasthenic syndrome, and myasthenia gravis. Each of these syndromes is associated with specific cancers.

- Paraneoplastic endocrine syndromes result from the secretion of hormone-like substances by tumor cells. Examples include Cushing syndrome, hypercalcemia, and SIADH.
- Paraneoplastic syndromes that affect the skin include acanthosis nigricans and the sign of Leser-Trélat. Both are associated with GI adenocarcinomas.
- Some paraneoplastic syndromes, such as SIADH, require specific, urgent treatment. Overall, however, the focus of treatment is the underlying malignancy.

## Review Questions

1. A 20-year-old female is brought to the emergency department by her roommate. The roommate says the patient has been acting bizarre lately, and she is afraid her friend might be taking psychedelic drugs. She also mentions that over the last few days, the patient had what she thought was the flu. The patient is admitted to the hospital, and a week later her blood pressure becomes unstable, she spikes a fever, and she becomes obtunded. Assuming this constellation of symptoms is all attributable to one underlying cancer, what malignancy would you be most concerned for?

- A. Gastric adenocarcinoma
- B. Lymphoma
- C. Ovarian teratoma
- D. Small cell lung cancer