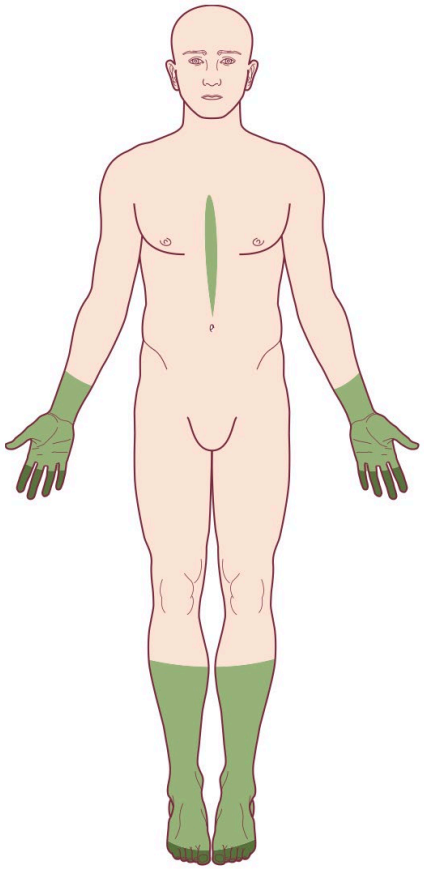
We would like to acknowledge that we are gathered today on the traditional territories of the Musqueam, Squamish and Tsleil-Waututh peoples.

Source: www.johomaps.net/na/canada/bc/vancouver/firstnations/firstnations.html

When should I worry about my patient's numbness and tingling in their limbs ?



VCH Family & Community Practice rounds

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March 25th, 2026

Disclosures

- None

Objectives

- Subacute (and acute) causes of peripheral neuropathy
- Brief approach to paraproteinemia and peripheral neuropathy
- When to expand the workup beyond the basic metabolic screen
- Red flags for alternative causes of numbness and tingling

Providing an overview on specific diseases but also a general approach

Please stop me anytime during the presentation if you have questions

I have integrated a few cases as well

“polyneuropathy," vs "peripheral neuropathy," vs "neuropathy"

Polyneuropathy refers to generalized process that affects multiple different nerves, ***predominantly*** affecting the distal nerves

Peripheral neuropathy usually used **synonymously** with polyneuropathy, but *technically* any disorder of the peripheral nervous system, which may include radiculopathies and mononeuropathies.

Neuropathy, even less specific term and can include disorders of the central and peripheral nervous system.

Clinical case

67-year-old man with a 3-month history of progressively worsening sensation of buzzing and tingling sensation in the feet but progressed over 1 week to his hands. He is also unsteady on his feet

PHMx is unremarkable but he consumes a “couple of beers” a day.

He takes vitamin supplementation but no other regular medications

He has no family history of neuromuscular disorders.

Clinical case

Neurological examination : reduced sensation to all sensory modalities (pinprick, temperature, vibration and proprioception) to mid-shins in legs and wrists in the arms. Strength was normal, and deep tendon reflexes were absent at the ankles.

Clinical case

What are the red flags in this case ?

- 3-month subacute progression
- Early involvement of the hands
- Early unsteadiness gait

Which vitamin supplementation is he taking ?

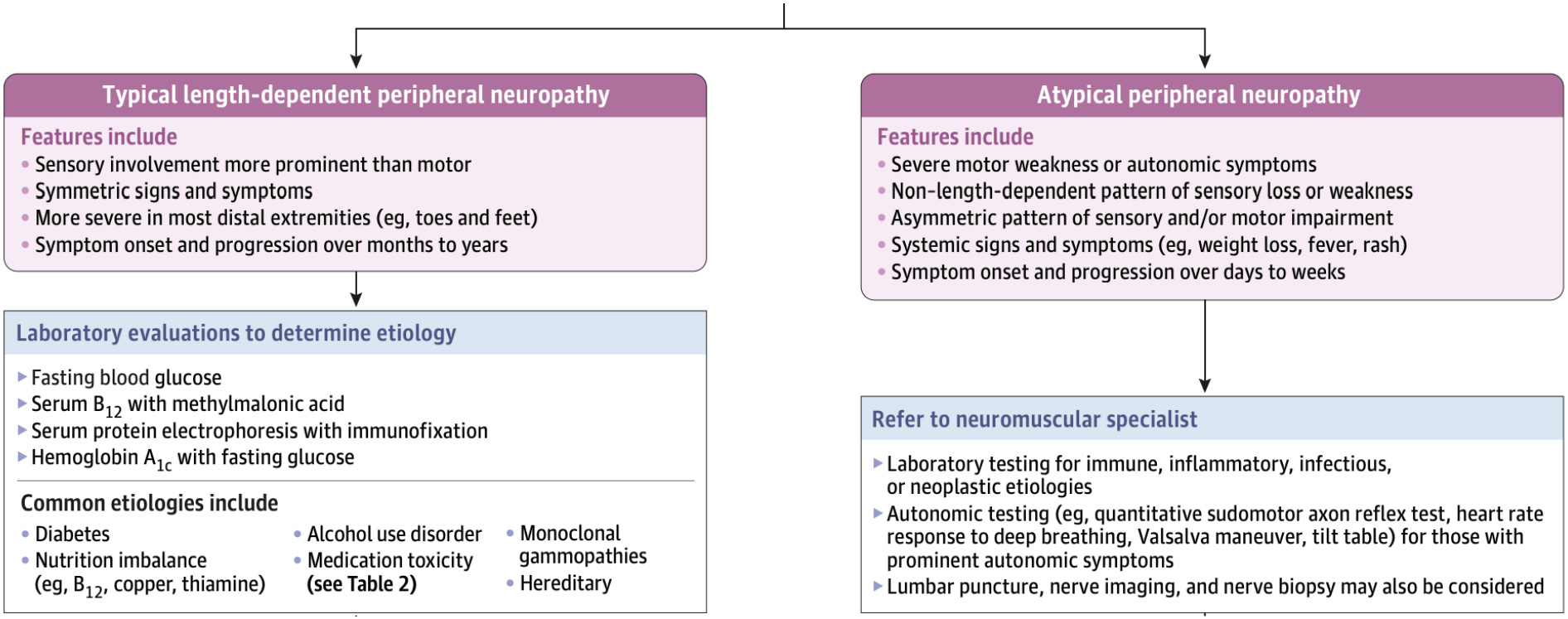
Clinical case

What are the red flags in this case ?

- 3-month subacute progression
- Early involvement of the hands
- Early unsteadiness gait
- Which vitamin supplementation is he taking ?

•Turns out he takes four tablets of a "daily nerve health supplement". Each tablet included **50 mg vitamin B6**, for a total daily dose of 200 mg.

Atypical/red flags features



Mauermann ML, Staff NP. JAMA. 2026;335(3):255-266. Figure 2.

Acute causes

Box 26–1. Acute Polyneuropathies

Guillain–Barré syndrome
Porphyria
Diphtheria
Drugs (e.g., dapsone, nitrofurantoin, vincristine)
Toxins (e.g., arsenic, thallium, triorthocresylphosphate)
Tick paralysis
Vasculitis

Preston DC, Shapiro BE. Electromyography and neuromuscular disorders. Elsevier/Saunders; 2013. Box 26-1.

Nitrofurantoin

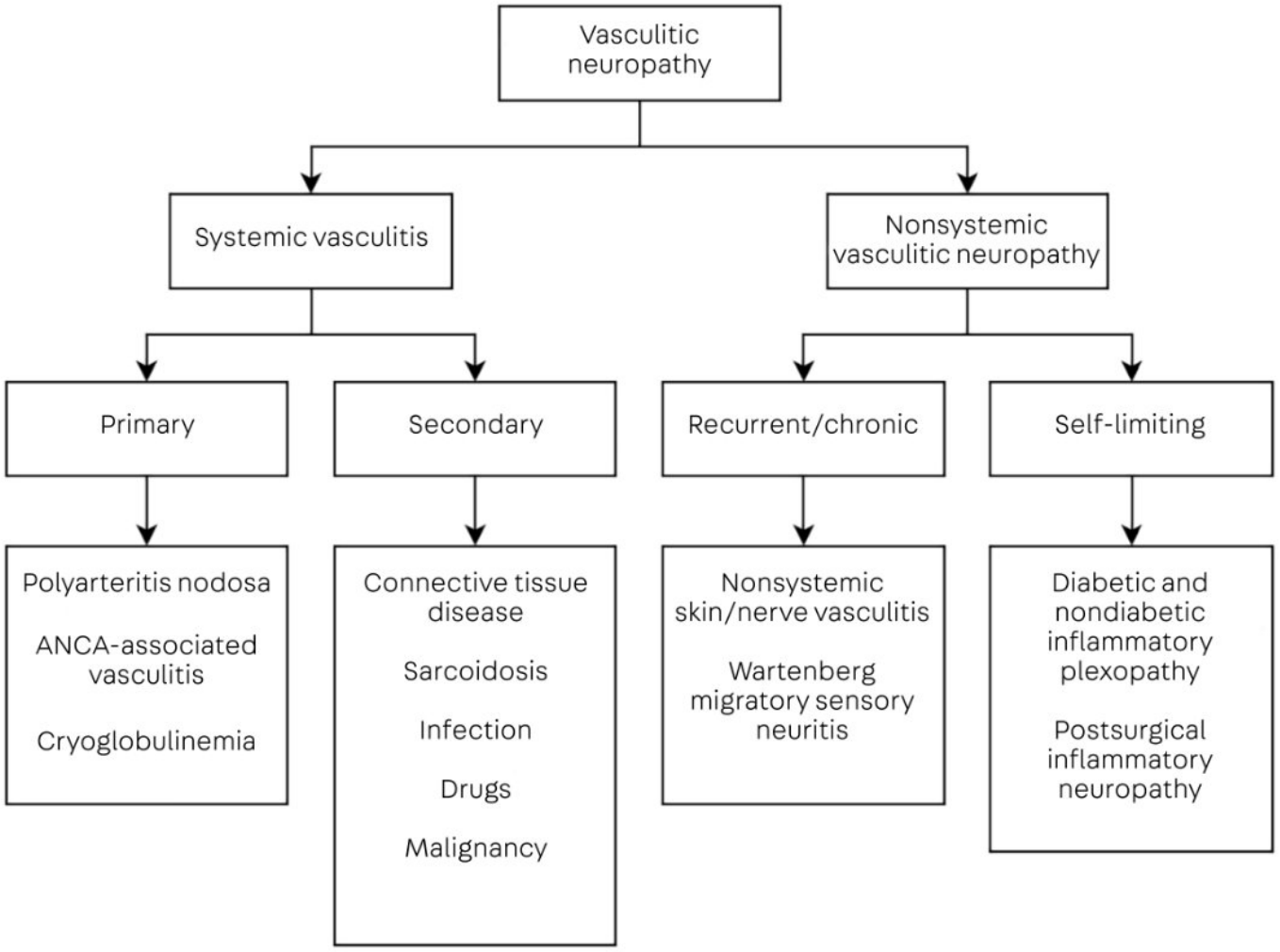
- Risk factor: Renal failure
- Neuropathy
  - Acute (*how many doses/days of therapy ??*)
    - Can be Motor predominant
  - Sensory: Paresthesias
  - Distribution: Distal > proximal; Symmetric
  - Recovery
    - Stop drug at 1st sign of neuropathy
    - **Often only partial**

Neuropathy:

Peripheral neuropathy, which may become severe or irreversible, has occurred. Fatalities have been reported. Conditions such as renal impairment (creatinine clearance under 60 mL per minute or clinically significant elevated serum creatinine), anemia, diabetes mellitus, electrolyte imbalance, vitamin B deficiency, and debilitating disease may enhance the occurrence of peripheral neuropathy. Patients receiving long-term therapy should be monitored periodically for changes in renal function.

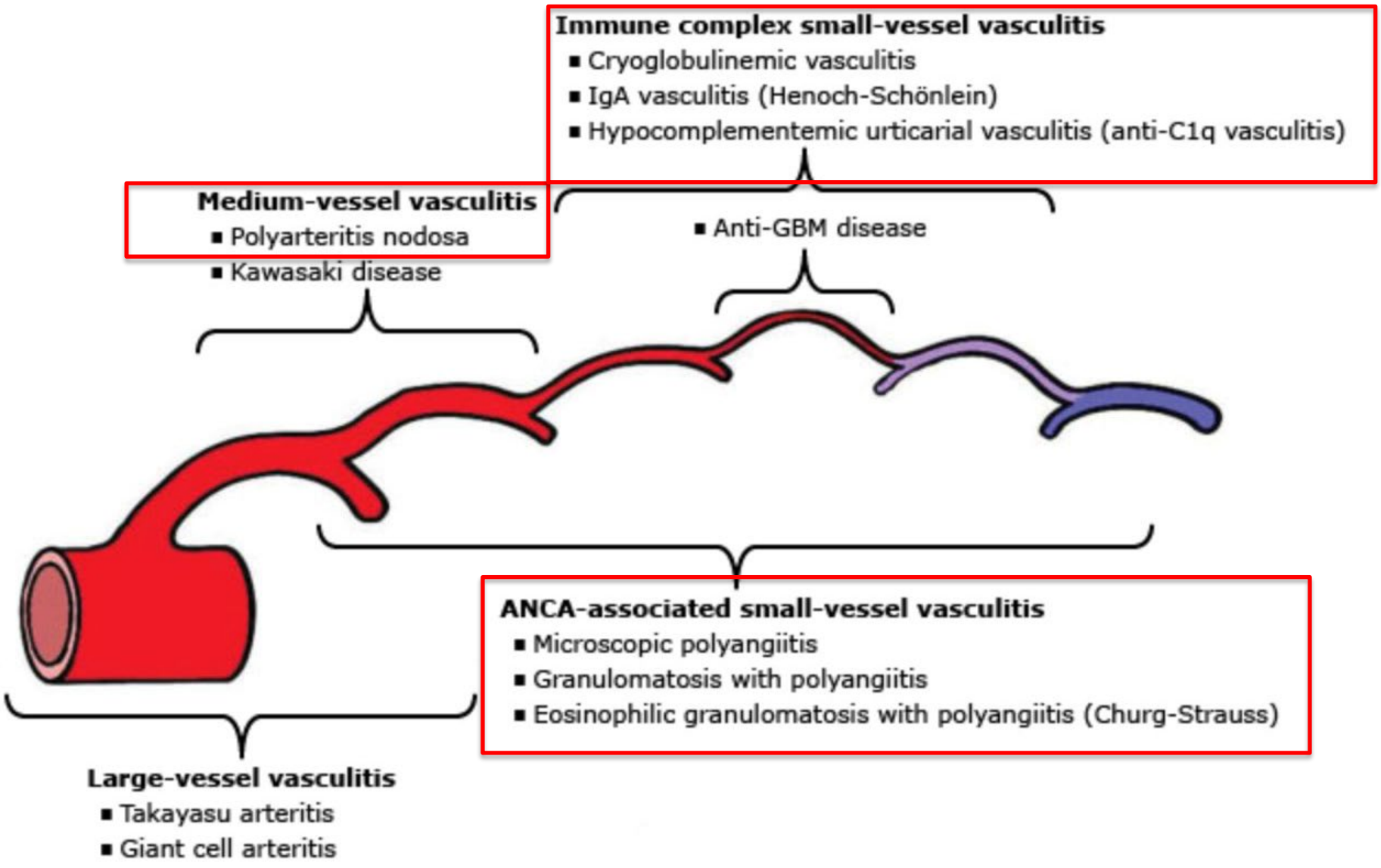
https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/020064Orig1s029lbl.pdf
https://neuromuscular.wustl.edu/nother/toxic.htm#nitrofurantoin

Vasculitic neuropathy



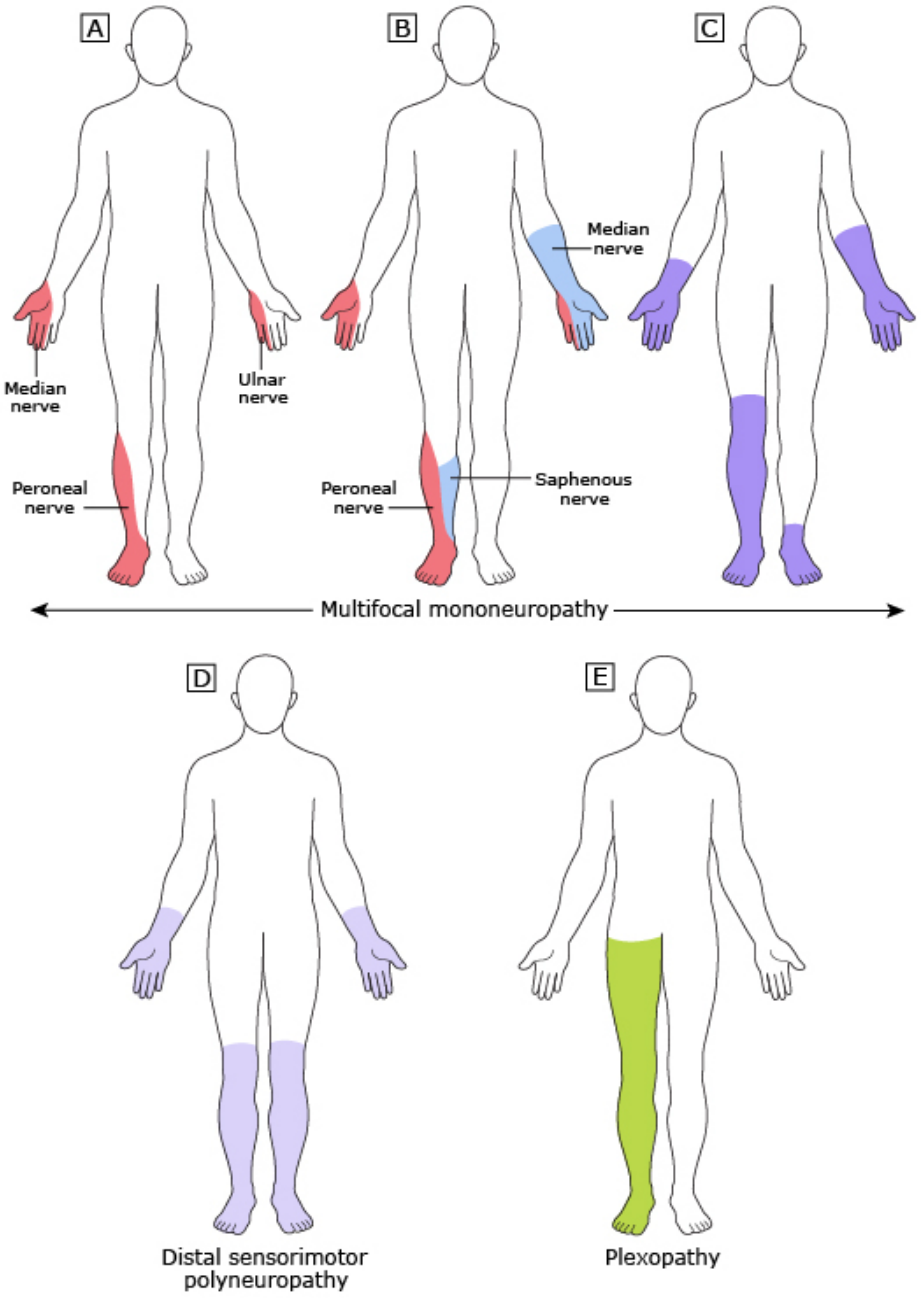
From: Continuum (Minneap Minn). 2020;26(5):1257-1279. Figure 6.1

Vasculitic neuropathy



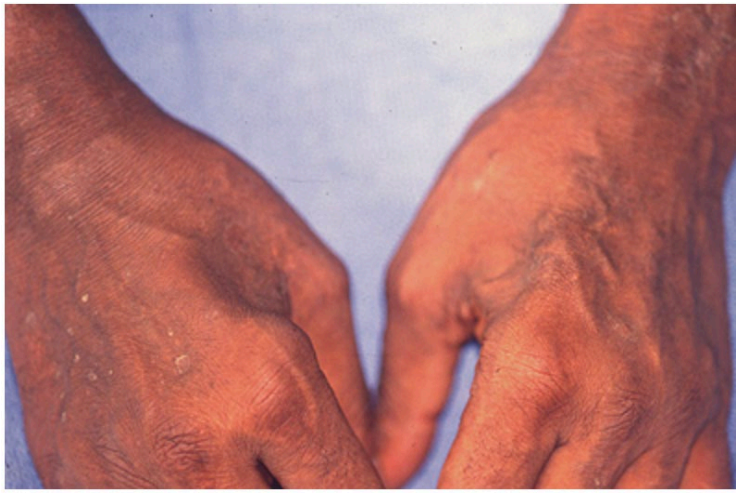
Collins MP, Dyck PJB. Vasculitic neuropathies. UpToDate. 2026. Graphic 96750 Version 5.0

Mononeuritis multiplex



Collins MP, Dyck PJB. Vasculitic neuropathies. UpToDate. 2026. Graphic 121154 Version 1.0

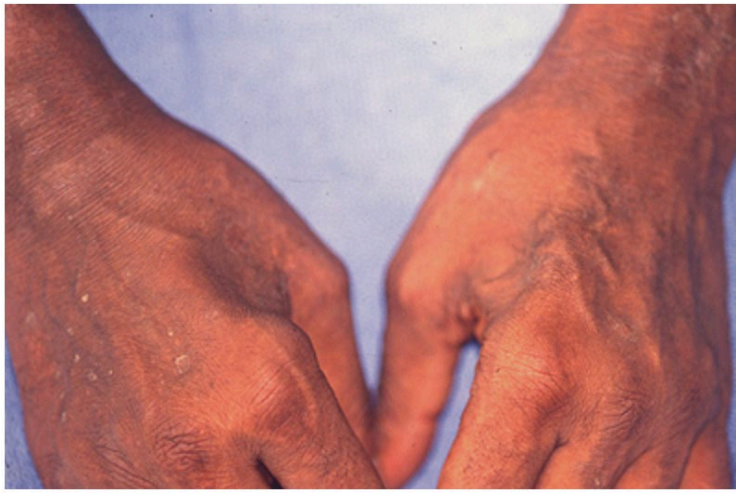
Mononeuritis multiplex



- Acute focal, painful neuropathy --> subacutely over days to weeks to involve other regions of the body
- **Asymmetrical** (legs often affected first)
- Pain is a sensitive feature and present in > 90 percent of patients
  - **Sharp achy pain** followed by more **typical neuropathic features** such as burning, tingling, and a warm/cold sensation

Collins MP, Dyck PJB. Vasculitic neuropathies. UpToDate. 2026. Graphic 51613 Version 1.0

Mononeuritis multiplex

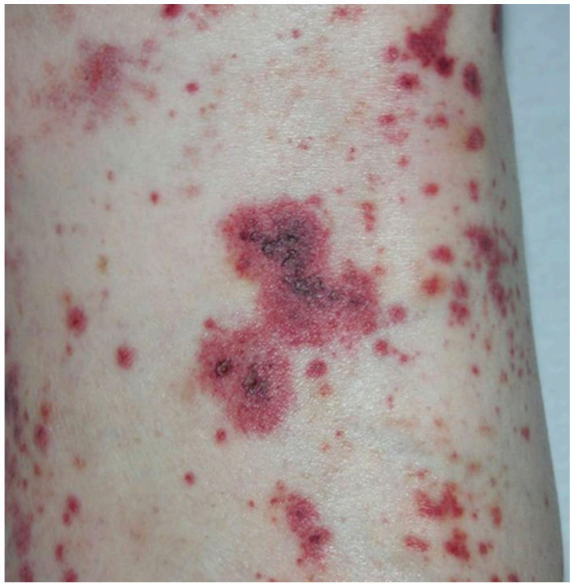


- **Fever, malaise, and weight loss** are present in most patients with **systemic vasculitis**.
- Less common and milder in patients with nonsystemic vasculitic neuropathy, with weight loss (30%) and fever (10-15%) still seen

Collins MP, Dyck PJB. Vasculitic neuropathies. UpToDate. 2026. Graphic 51613 Version 1.0

Mononeuritis multiplex
Systemic vasculitis

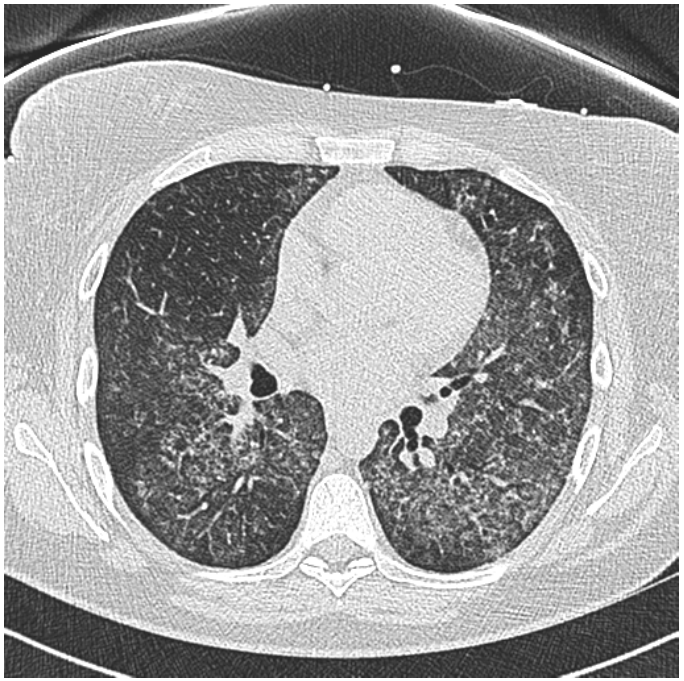
- **Palpable purpura or skin ulcers** seen in small- or medium-vessel vasculitis (such as **granulomatosis with polyangiitis [GPA]**)



Collins MP, Dyck PJB. Vasculitic neuropathies. UpToDate. 2026. Graphic 51770 Version 2.0

Mononeuritis multiplex
Systemic vasculitis

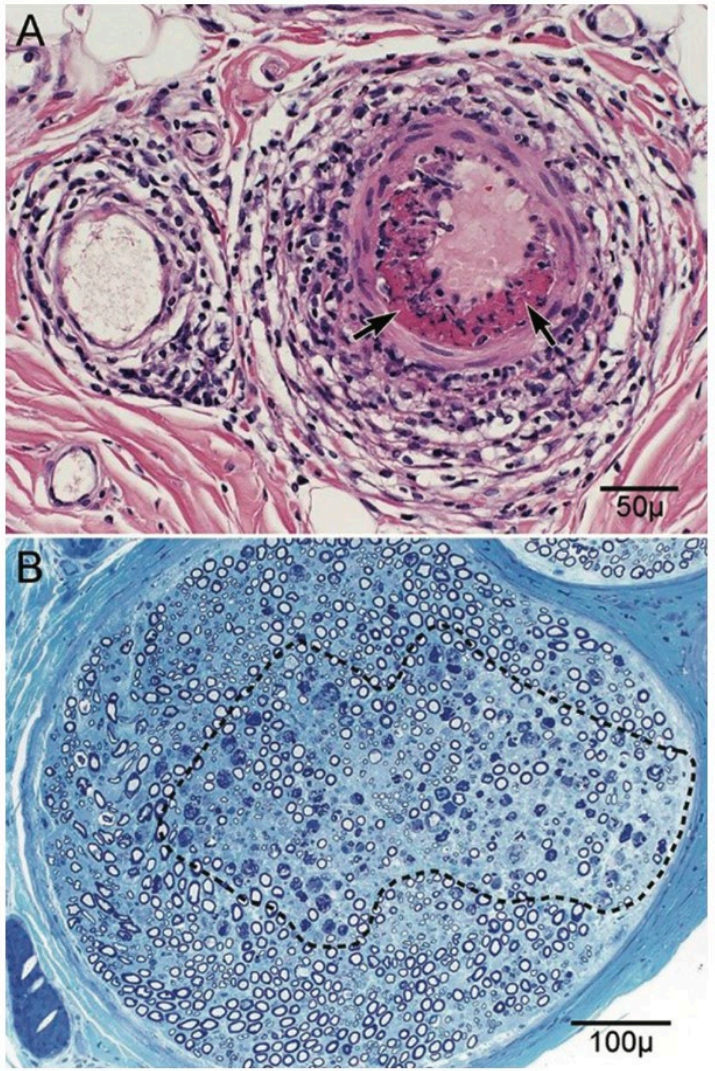
- Destructive upper airway lesions in GPA;
- Asthma, allergic rhinitis, and/or nasal polyps in eosinophilic granulomatosis with polyangiitis [EGPA; Churg-Strauss]
- Alveolar hemorrhage in all forms



Radiopaedia.org. Diffuse alveolar hemorrhage [Internet]. Radiopaedia.org; [cited 2026 Mar 21]. Available fro
https://radiopaedia.org/articles/diffuse-alveolar-hemorrhage

Diagnosis of vasculitic neuropathy

- Nerve biopsy is **required** for diagnosis ***(nuanced in systemic vasculitis)***
- Intramural inflammation accompanied by pathologic evidence of vascular wall damage
- Sensitivity is only about 50%.. 65% when combined with muscle biopsy



From: Continuum (Minneap Minn). 2020;26(5):1257-1279. Figure 6.3

Nonsystemic vasculitic neuropathy

- Requires **URGENT** **treatment**
- **High-dose glucocorticoids plus glucocorticoid-sparing agent**

-azathioprine vs methotrexate vs cyclophosphamide

Back to our case...

Clinical case

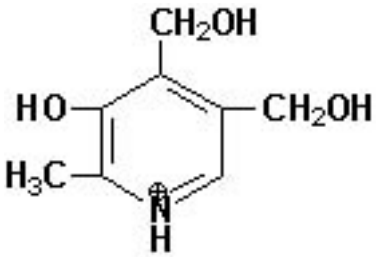
What are the red flags in this case ?

- 3-month subacute progression
- Early involvement of the hands
- Early unsteadiness gait

- **Which vitamin supplementation is he taking ?**
  - **Turns out he takes our tablets of a "daily nerve health supplement". Each tablet included 50 mg vitamin B6, for a total daily dose of 200 mg.**

Metabolic cases

B6 (pyridoxine) toxicity

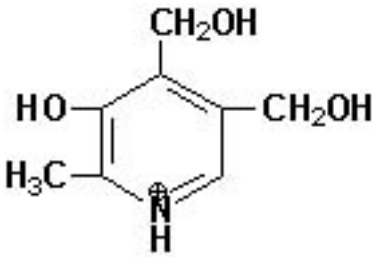


- Direct damage to the **dorsal root ganglia (DRG)** sensory neurons
- Irreversible ganglionopathy that may worsen for weeks following discontinuation of vitamin B6
  - sensory ataxia with unsteady gait and pseudoathetoid posturing

- Toxicity with excessive supplementation usually more than 2 g/d, but long-standing (> 6 months) use of 50 mg/d also describes in the literature
- *My general rule is no more than 50 mg/d if needed for as short as possible (cramps for example)*

Metabolic cases

B6 (pyridoxine) deficiency



- Deficiency due to poor oral intake is **uncommon**
- Occurs most commonly with isoniazid use for TB treatment (standard of care to provide supplementation during treatment)
- Sensory-predominant axonal length-dependent peripheral neuropathy
- Replacement therapy for vitamin B6 deficiency is 50 mg/d orally **(if CLEAR deficiency present)**

Clinical case

- A 19-year-old female presenting with difficulty walking and leg numbness over 1 week. She noted foot drop and paresthesia in her hands as well. Urinary urgency present. Neurological review of systems negative otherwise
- No systemic symptoms.
- Studies political sciences in University.
- Denies THC, ETOH, smoking cigarettes

Clinical case

EXAM

- Upper limb examination was normal.
- Lower limb strength severe weakness of ankle dorsiflexion and eversion and mild weakness of plantarflexion and inversion.
- Lower limb reflexes were absent and the right plantar was upgoing.
- He had reduced pinprick perception to the ankles with reduced vibration sense and proprioception at the toes.

Clinical case

- What other questions may we ask here ?

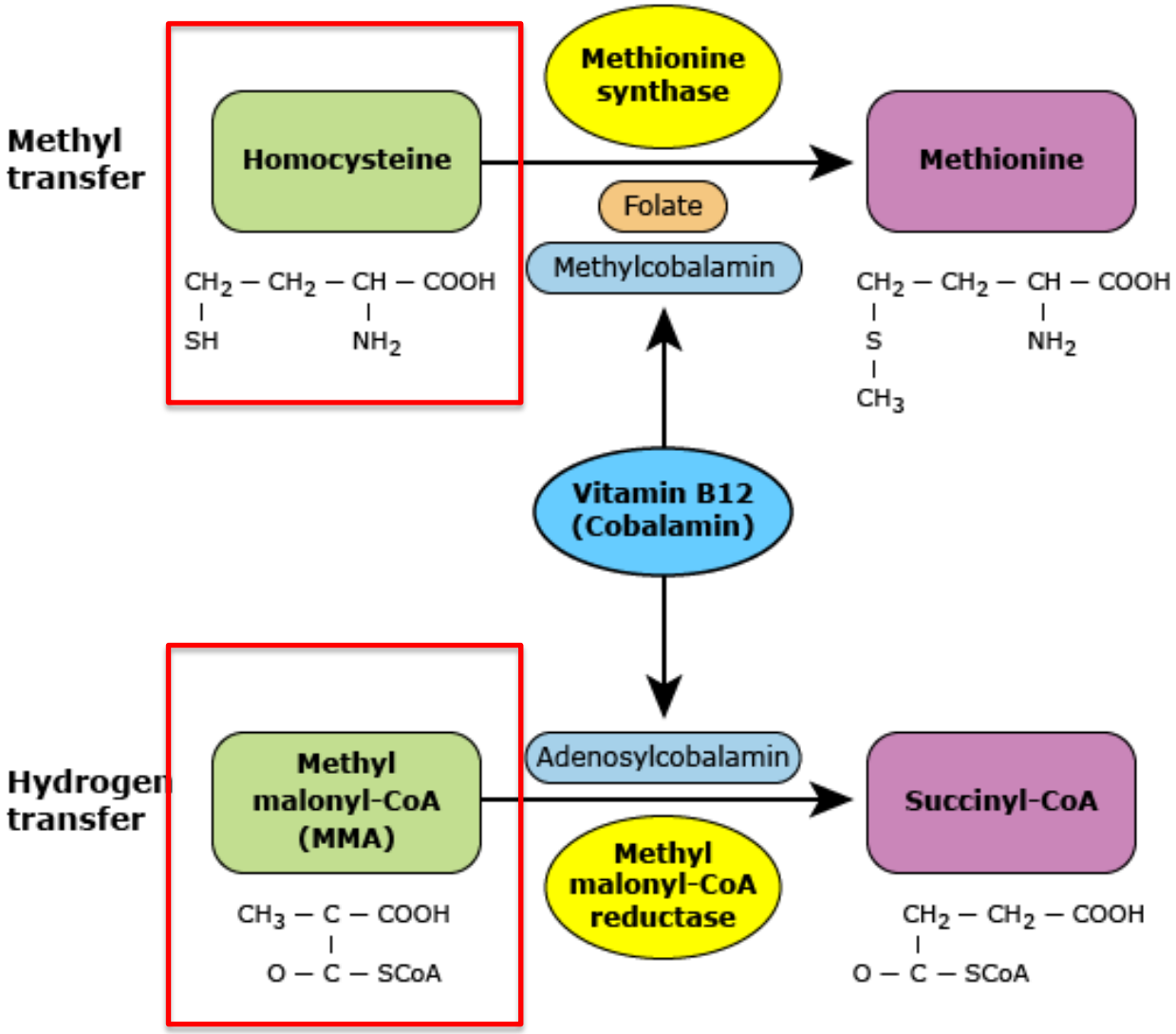
Clinical case

- On **specific questioning,** reports using nitrous oxide for the past 5 years and was using up to 60 bottles per day at presentation

- Vitamin B12 level normal at 300 ; **next steps ?**

Metabolic cases

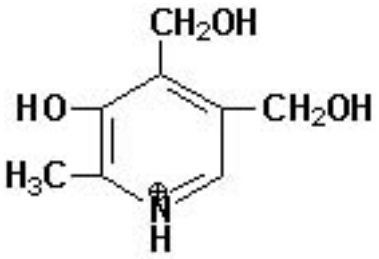
B12



Source: Means RT Jr, Fairfield KM. Clinical manifestations and diagnosis of vitamin B12 and folate deficiency. UpToDate. Accessed Ma 21, 2026. Graphic 139892 Version 3.0

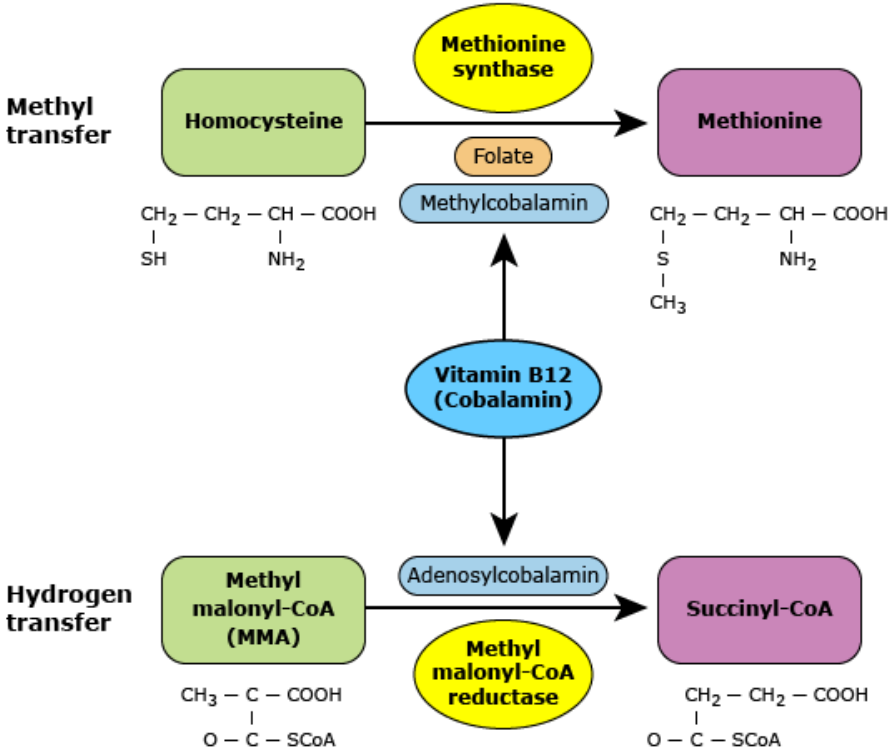
Metabolic cases

B12



Risk factors

- Strict vegan diet.
- Poor gastrointestinal absorption : atrophic gastritis, gastric bypass, prolonged proton pump inhibitor use, pernicious anemia, IBD such as Crohn disease, surgical resection of the ileum
- **Nitrous oxide causes functional Vitamin B12 deficiency**

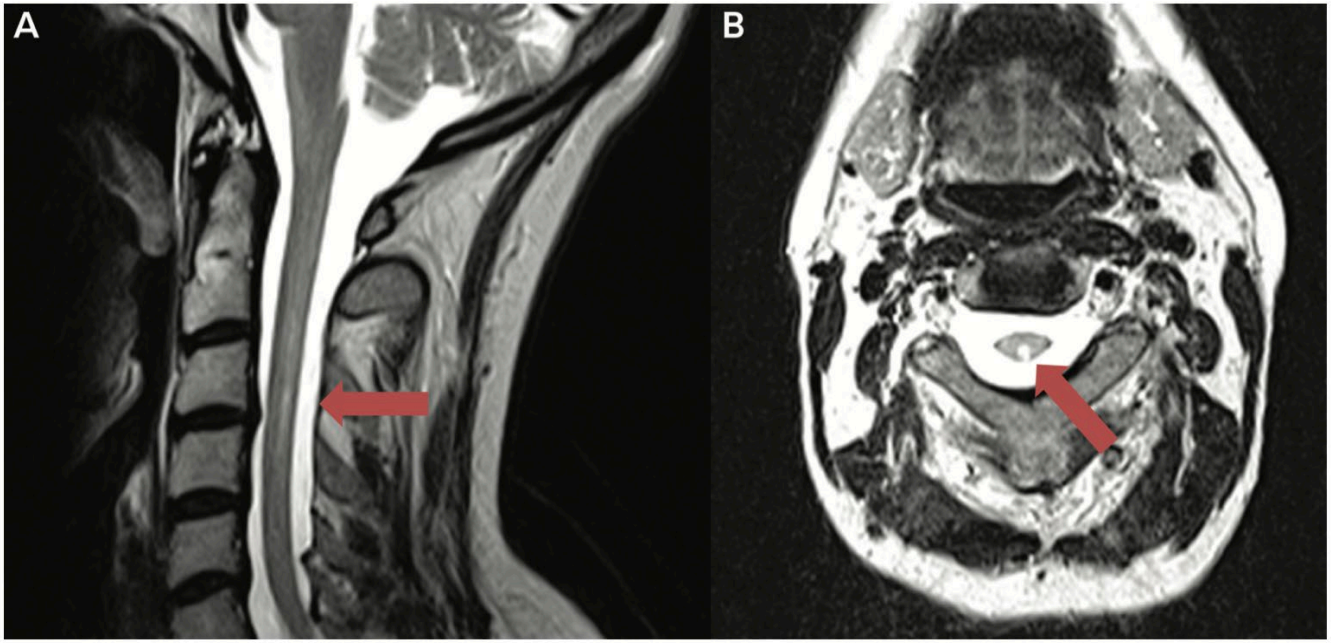


Source: Means RT Jr, Fairfield KM. Clinical manifestations and diagnosis of vitamin B12 and folate deficiency. UpToDate. Accessed Ma 21, 2026. Graphic 139892 Version 3.0

Metabolic cases

B12

- *"subacute combined degeneration of the spinal cord"*
- Classic triad of **sensory ataxia, posterior column dysfunction**, and **spastic paraparesis**
- Mixed upper and lower motor neuron signs (absent ankle reflexes with upgoing toe).



Metabolic cases

B12

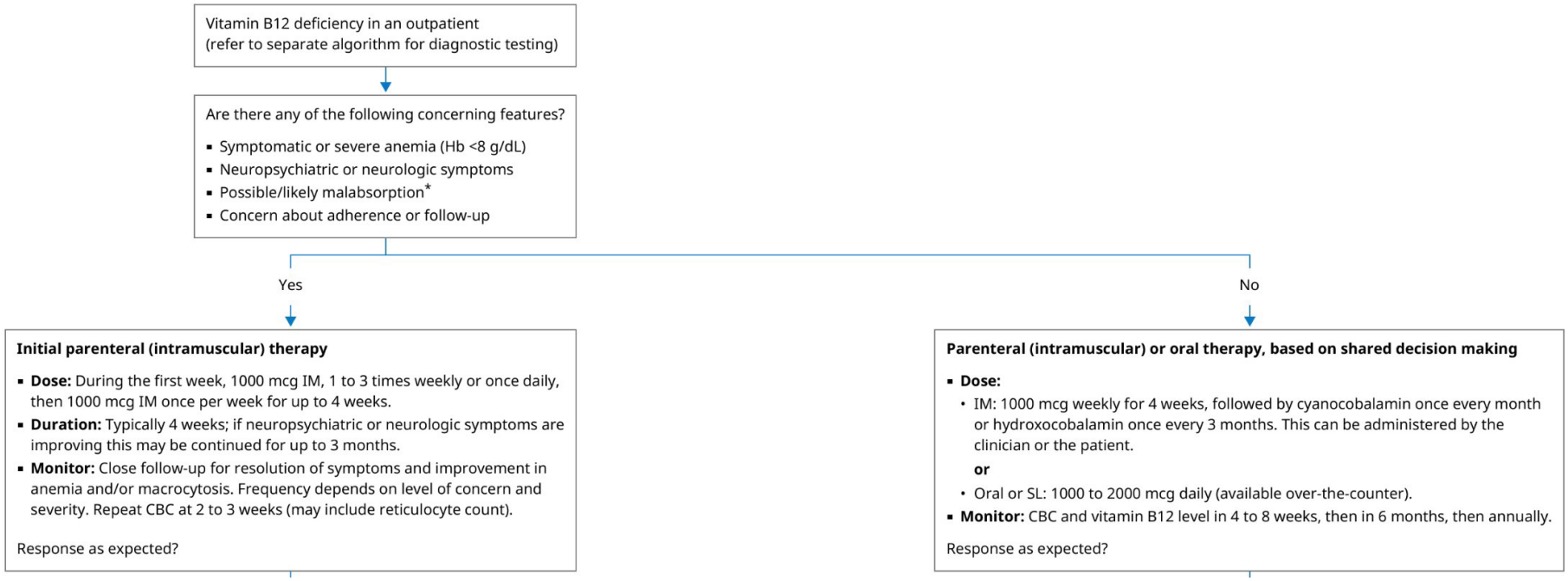
MMA and homocysteine normal – No deficiency of vitamin B12 or folate.

MMA and homocysteine elevated – Deficiency of vitamin B12 (some normal homocysteine and elevated MMA)

MMA normal, homocysteine elevated – No deficiency of vitamin B12. Could be deficiency of folate but not diagnostic.

Metabolic cases

B12



Means RT Jr, Fairfield KM. UpToDate. Graphic 131424 Version 10.0. Accessed Mar 21, 2026.

Metabolic/toxic

Nitrous Oxide

Nitrous oxide oxidizes cobalt ions in vitamin B12 (cobalamin), resulting in inactive methylcobalamin (a physiologically active form of B12)

EMG/NCS - May lead an acute or subacute onset distal and motor predominant axonal neuropathy

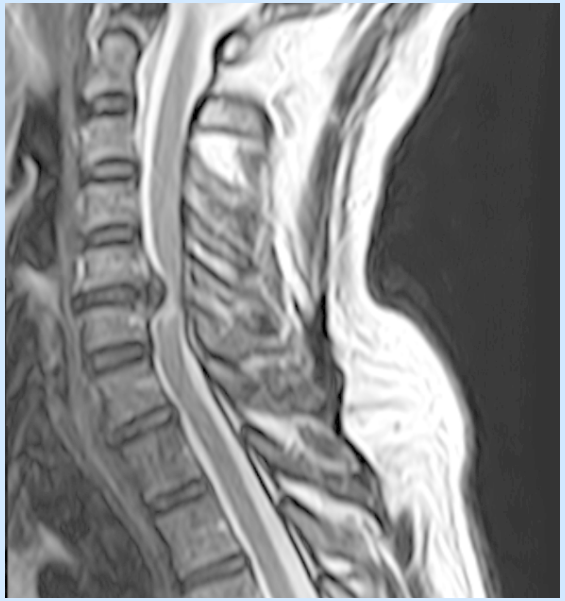
Treatment :

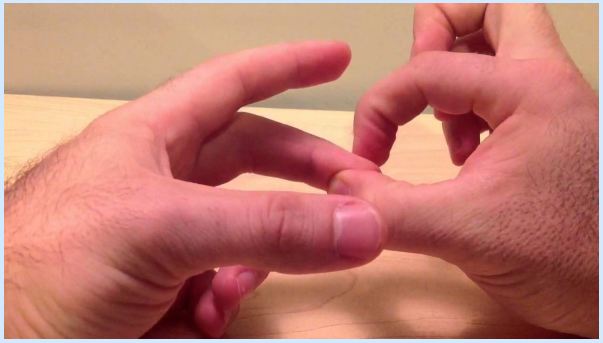
- **STOP nitrous oxide**
- High-dose intramuscular B12 (eg, 1mg every 2 days for 11 doses), followed by long-term replacement
- Neurological recovery can often be slow and may be incomplete

https://health.clevelandclinic.org/what-are-whippets

Red flags for cervical MYELOPATHY

- Early onset of sensory symptoms in the hands
- Early issues with dexterity
- B/B dysfunction
- Pyramidal distribution of weakness (preferential weakness of upper limb extensors and lower limb flexors)
- Brisk reflexes (look for Hoffman's sign, upgoing toes)
- Gait instability early on





Toxic causes

Alcohol

- About 46% in individuals with chronic AUD
- Usually, length dependent sensorimotor polyneuropathy
- Direct alcohol toxicity and vitamin deficiencies
- **** common cause of SMALL fiber neuropathy ****
- Advice all patients with polyneuropathy to reduce and stop ETOH

https://magazine.medlineplus.gov/article/alcohols-health-effects-what-you-need-to-know

Case #3

- 42 y.o male with 3-month history of swelling in feet and difficulty lifting his right leg going upstairs.
- Over a matter of a few weeks, symptoms evolved to diffuse limb weakness and sensory loss spreading from toes to knees.
- Also reports erectile dysfunction, intermittent bouts of severe abdominal pain

Case #3

- Exam showed LE swelling, flushing and UE hypertrichosis, palpable axillary and inguinal adenopathy, hepatosplenomegaly
- Diffuse weakness distal > proximal, LE > UE
- Hyporeflexic in the upper limbs and areflexic in the lower limbs.
- Sensation reduced to vibration, joint position, and pinprick below the knees
- Positive Romberg sign

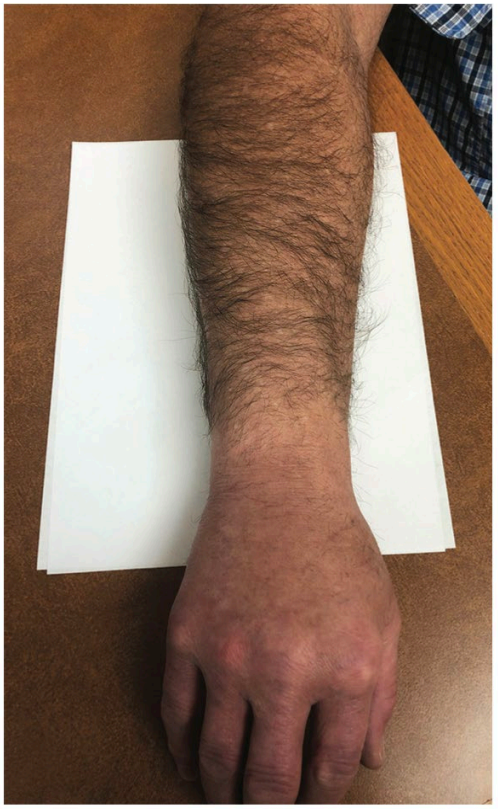


Figure 11-3. Continuum (Minneap Minn). 2020;26(5, Peripheral Nerve and Motor Neuron Disorders):1369-1383.

Case #3

Next steps ?

Case #3

Broad workup important given the several red flags

Case #3

Platelets : 1349
SPEP/UPEP normal

Serum free light chains :
Kappa light chains: 23.9 mg/L
Normal range: 3.3-19.4 mg/L
Lambda light chains: 84.7 mg/L
Normal range: 5.7-26.3 mg/L
Kappa to lambda ratio: 0.28
Normal range: 0.26-1.65

Case #3

NCS : axonal greater than demyelinating length-dependent peripheral neuropathy without evidence of conduction block or temporal dispersion.

Case #3

Any initial thoughts ?
Any other investigations ?

Case #3

LP – protein 2.35 g/L (VERY high)
CT abdo/pelvis : moderate splenomegaly with three nonspecific bone lesions felt to be benign.

Case #3

Trial of IVIG for a **presumed diagnosis of CIDP** – no clinical improvement

PET CT scan : expansile lytic lesion in the right ilium and right midhumerus and prominent fludeoxyglucose (FDG)-avid right axillary lymph nodes.

VEGF level very high (700 pg/mL, normal <96.2 pg/mL)

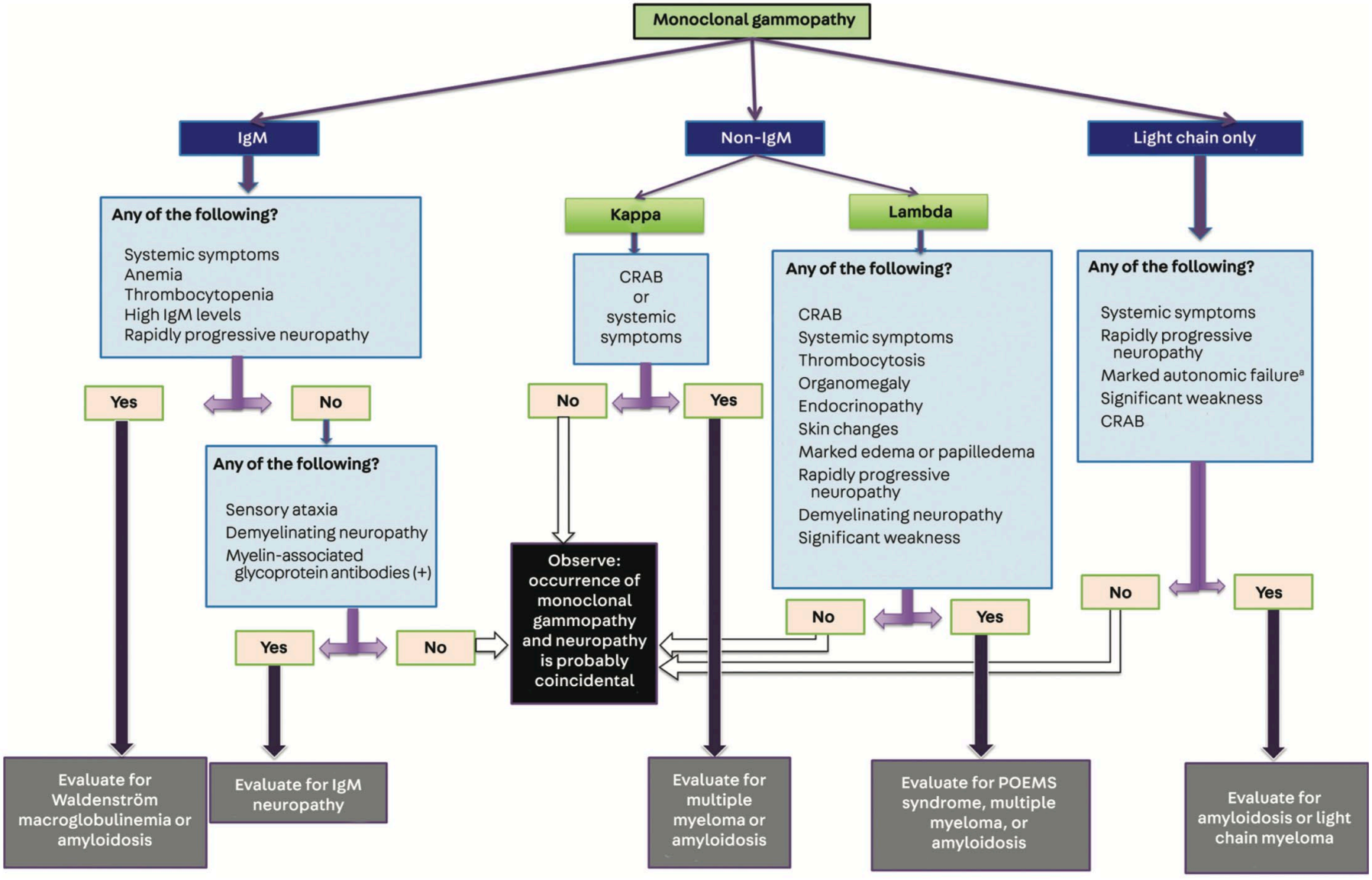
Bone marrow biopsy - 20% lambda light chain restricted plasma cells

Case #3

Final diagnosis ?

POEMS [polyneuropathy, organomegaly, endocrinopathy,monoclonal gammopathy, and skin changes] syndrome)

Monoclonal gammopathy and neuropathy



Continuum (Minneap Minn). 2020;26(5, Peripheral Nerve and Motor Neuron Disorders):1369-1383. Figure 11-2

Monoclonal gammopathy and neuropathy

- **10% of patients** with PN have a monoclonal gammopathy (after NCS/EMG) (but most are incidental)
- More common with **IgM** than with IgA or IgG monoclonal proteins.
- Monoclonal gammopathies occur in 3.2% of individuals older than 50 years and in 5% of those older than 70 years. **Their coexistence with PN may be coincidental.**
- Still referred to hematology for evaluation of plasma cell disorders
- **I tend to order SPEP/UPEP with all patients with neuropathy but is it truly mandatory ?**

POEMS (POLYNEUROPATHY, ORGANOMEGALY, ENDOCRINOPATHY, MONOCLONAL PLASMA CELL DISORDER, AND SKIN CHANGES)

Table 1 Diagnostic criteria for POEMS syndrome

Criteria	
Mandatory major criteria	1. Polyneuropathy 2. Monoclonal plasma cell proliferative disorder
Other major criteria (one required)	3. Castleman's disease 4. Sclerotic bone lesions 5. Raised vascular endothelial growth factor
Minor criteria	6. Organomegaly (spleen/liver/lymph nodes) 7. Extravascular volume overload 8. Endocrinopathy (adrenal, thyroid*, pituitary, gonadal, parathyroid, pancreatic*) 9. Skin changes 10. Papilloedema 11. Thrombocytosis/polycythaemia
Other useful features	Clubbing, weight loss, hyperhidrosis, pulmonary hypertension/restrictive lung disease, thrombotic diathesis, diarrhoea, low serum, vitamin B_{12}

*Due to high prevalence of thyroid disease and diabetes mellitus, this diagnosis alone is not sufficient to meet the criteria for endocrinopathy. POEMS, polyneuropathy, organomegaly, endocrinopathy, the presence of a monoclonal plasma cell disorder and skin disease.

Keddie S, et al. Pract Neurol. 2018;18(4):278-290. Table 1

POEMS - Neuropathy

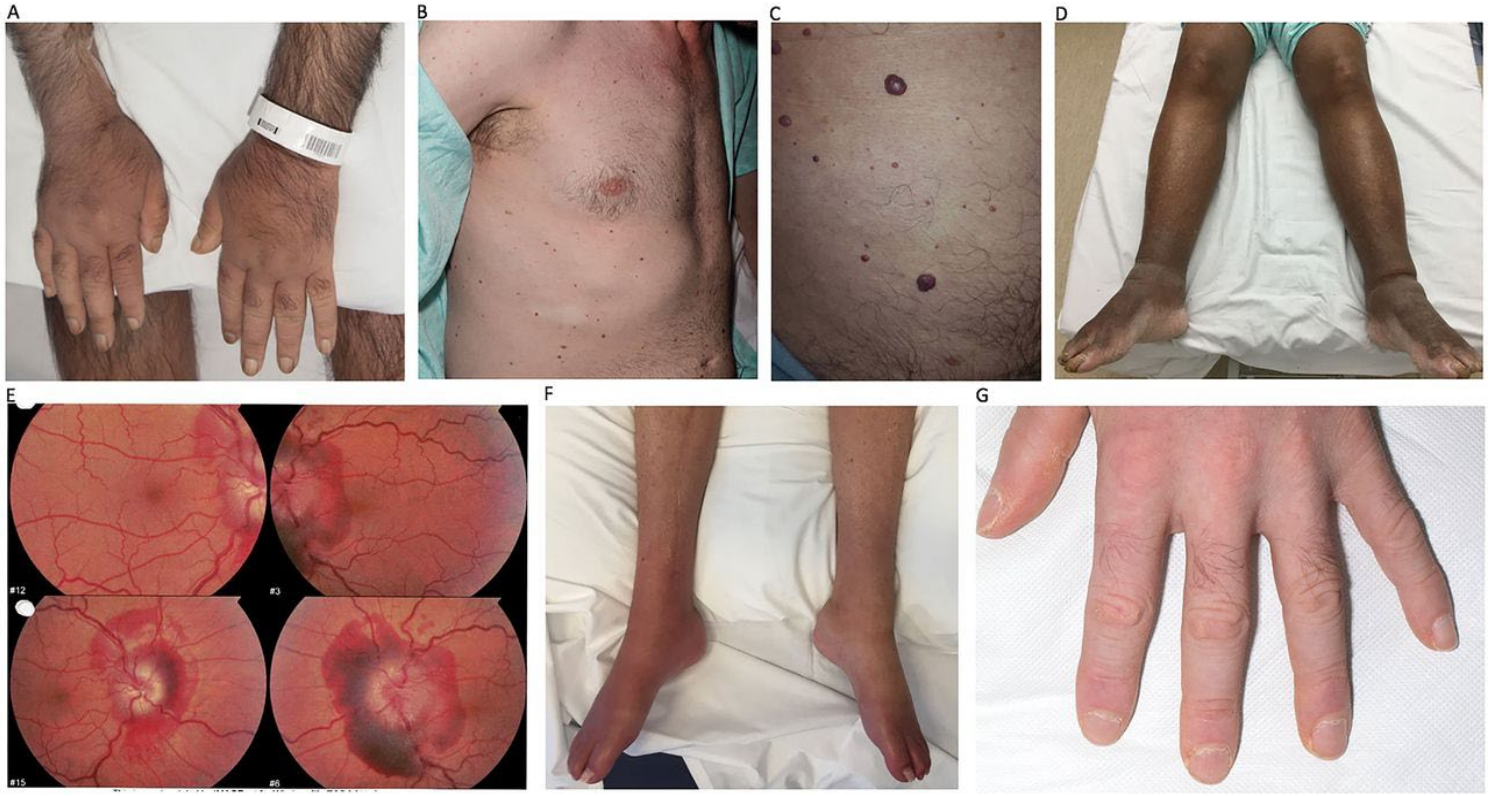
Clinical : Starts distally lower limbs with weakness (often severe) and sensory loss --> rapid progression to a **polyradiculoneuropathy** with proximal and distal weakness and loss of reflexes

Pain is common (less common in CIDP)

Nerve conduction studies shows primarily demyelinating length-dependent sensorimotor peripheral neuropathy vs diffuse polyradiculoneuropathy

Less autonomic involvement but erectile dysfunction

POEMS – Key findings



Keddie S, et al. Pract Neurol. 2018;18(4):278-290. Figure 1

IgM MGUS

- DADS- distal acquired demyelinating symmetric neuropathy (DADS-M)
  - Usually presents with distal but slowly progressive sensory loss in feet that can result in gait ataxia and sometimes tremor
  - No weakness or minimal (toe extension)
  - Sometimes can look like CIDP – more prominent weakness

DADS (distal acquired demyelinating symmetric neuropathy)

- 50%-75% will have anti-MAG antibodies **(DADS-M)**
- 33-64% of patients with DADS do NOT have a monoclonal protein **(DADS-I).**
- DADS-I responds to CIDP immunotherapy such as IVIG
- DADS-M less responsive and if insidious course, then I follow them clinically

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Finish line

THE UNIVERSITY OF BRITISH COLUMBIA