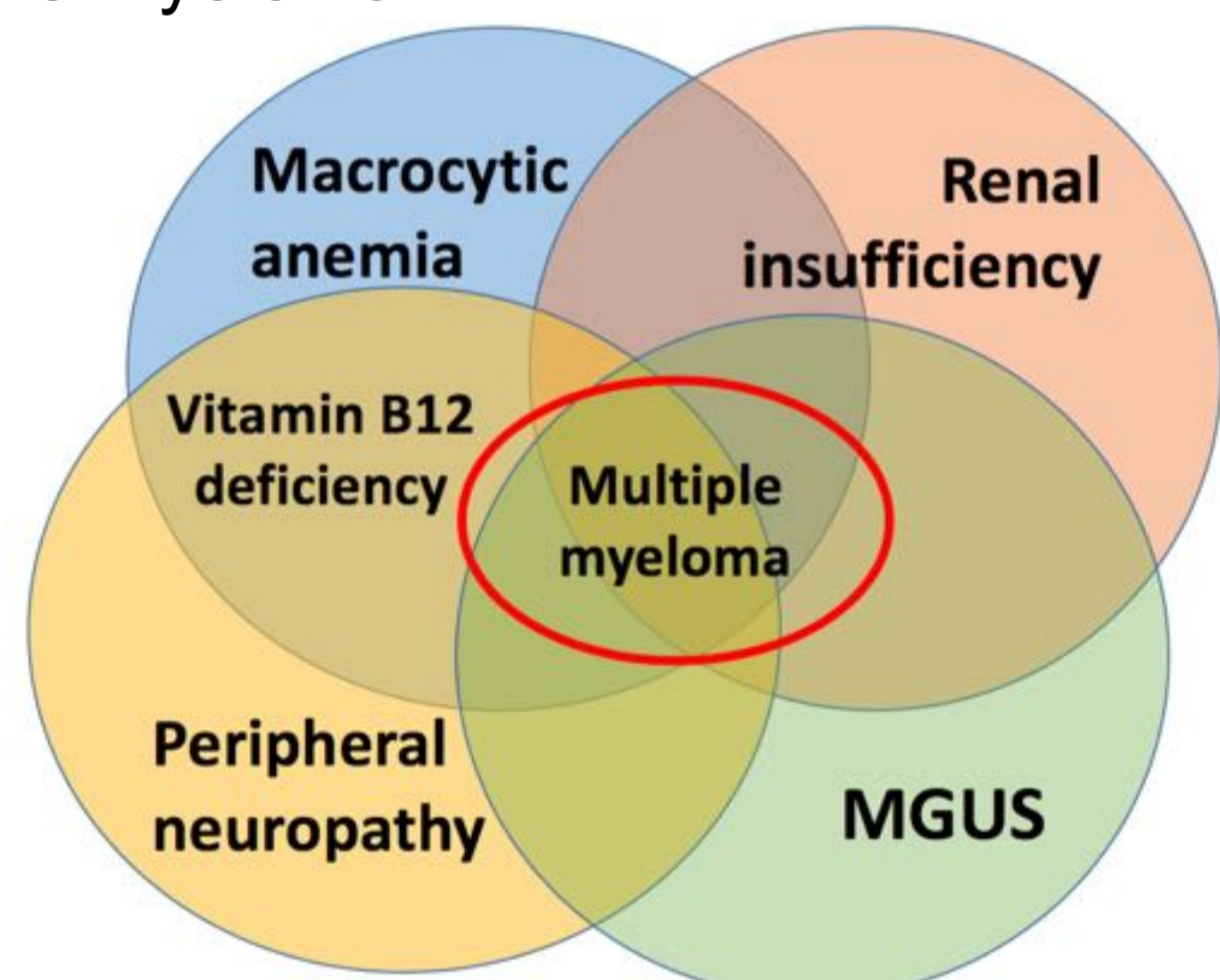


PERIPHERAL NEUROPATHY AND MACROCYTIC ANEMIA: A NEAR MISS

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CASE DESCRIPTION

- Presentation:** an 83-year-old man with a PMH of CVA, sinusitis, vitamin B12 deficiency and MGUS presented with chronic progressive fatigue, dyspnea, stocking-glove peripheral neuropathy, and impaired gait.
- Initial labs:** new renal insufficiency (Cr 2.1), new macrocytic anemia (Hgb 7.4, MCV 109), and mild eosinophilia.
- Problem representation:** elderly man with PMH of MGUS and vitamin B12 deficiency who presents with progressive dyspnea, stocking-glove peripheral neuropathy, and fatigue, who was found to have acute on chronic macrocytic anemia and renal insufficiency, concerning for multiple myeloma.



- Differential diagnosis:** multiple myeloma, myelodysplastic syndrome, vitamin B12 deficiency, strongyloidiasis, and EGPA.

INITIAL MANAGEMENT

- Work-up:** due to high suspicion for multiple myeloma, initial work-up included SPEP, UPEP, serum free light chains, and quantitative immunoglobulins. After discharge, multiple myeloma work-up was negative. Vitamin B12 levels showed partially treated vitamin B12 deficiency.
- Working diagnosis:** vitamin B12 deficiency with possible myelodysplastic syndrome.
- Plan:** replete vitamin B12 more aggressively and follow-up with outpatient bone marrow biopsy.

NEAR MISS & FINAL DIAGNOSIS

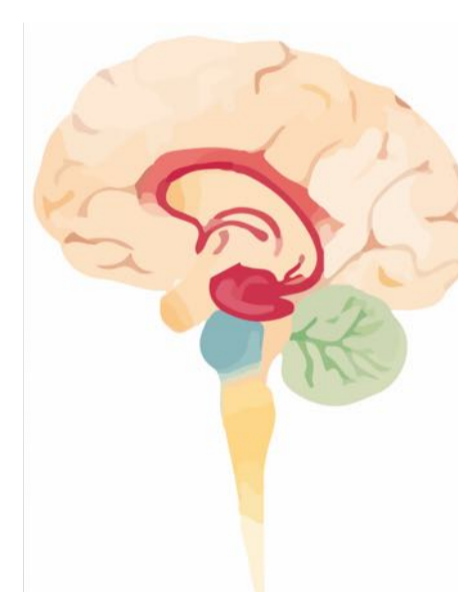
- Only when this case was discussed during noon report one week later, it came to light that the patient's constellation of symptoms could all be explained by copper deficiency, and that patient's undetectable copper level was previously missed by our team.

COPPER DEFICIENCY

- Copper deficiency is well documented but relatively rare. Recognizing copper deficiency is important, as it is a potentially devastating but treatable condition.
- Unlike folate and vitamin B12 deficiencies, many clinicians do not include copper deficiency in their differential diagnosis for myelodysplasia or neuropathy. Copper deficiency can masquerade as other conditions, such as multiple myeloma, myelodysplastic syndrome, or vitamin B12 deficiency.

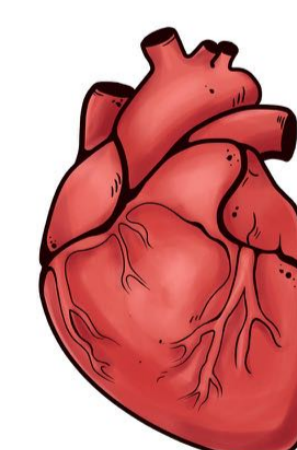
Signs

- Neurological:**
 - Peripheral neuropathy
 - Ataxia
 - Myelopathy
 - Optic neuropathy
- Hematological:**
 - Anemia
 - Leukopenia
 - Neutropenia
 - Dysplastic hematopoiesis with or without ring sideroblasts



Cardiovascular:

- Hypercholesterolemia
- Ischemic heart disease
- Stroke
- MI



Musculoskeletal:

- Low bone mineral density
- Impaired growth in children



Risk factors

- Gastrointestinal:**
 - Previous upper bowel resection/bariatric surgery
 - IBD
 - Chronic diarrhea
 - Short bowel syndrome
 - Cystic fibrosis



Medications:

- PPI use



Excess Zinc:

- Overuse of zinc supplements
- Ingestion of dental fixatives

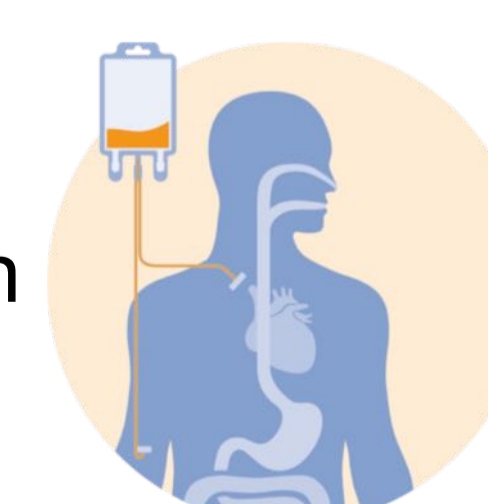


Metabolic:

- Menkes disease

Nutritional:

- Decreased consumption of copper-rich foods
- TPN



- In this case, we hypothesized that excess dental zinc paste ingestion caused copper malabsorption leading to copper deficiency.
- Excessive zinc intake causes upregulation of metallothionein (MT), resulting in the trapping of copper within intestinal cells. Sloughing of these enterocytes eventually leads to depletion of copper stores (pathophysiology figure).

PATHOPHYSIOLOGY

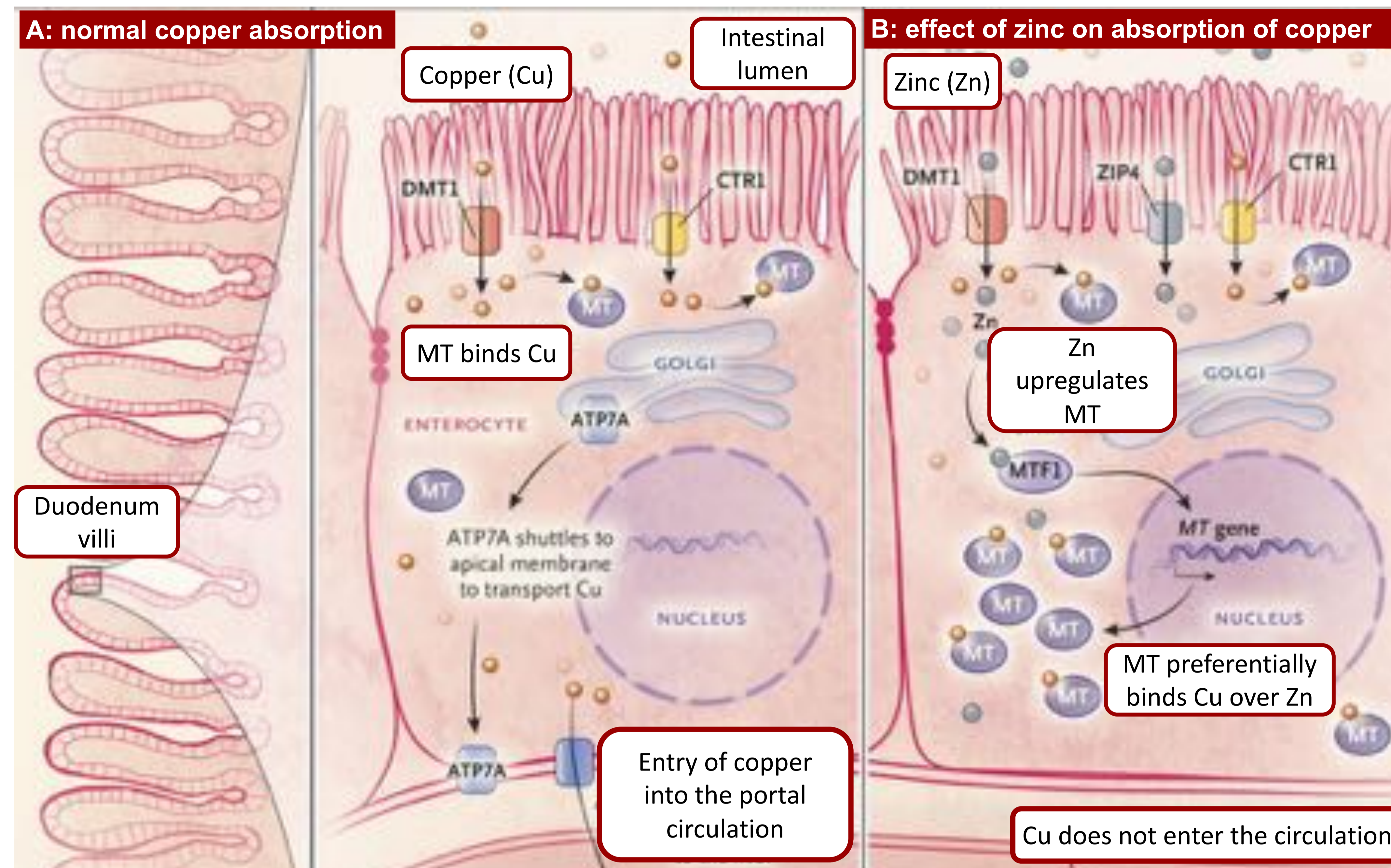


Figure: normal copper absorption (A), and the effect of zinc on the enteral absorption of copper (B). N Engl J Med 2017; 377:1379-1385

COGNITIVE ERRORS

- Availability bias** seeks a diagnosis which is easily retrievable because it is common or severe. We considered renal insufficiency, peripheral neuropathy, and anemia in a patient with MGUS as clues for multiple myeloma, as it fits its commonly used illness script, and can have severe implications when missed.
- Confirmation bias** seeks evidence that supports one's original hypothesis. Here, we found literature describing the link between multiple myeloma, B12 deficiency and pernicious anemia, and therefore attributed vitamin B12 deficiency to multiple myeloma.
- Anchoring bias** refers to the error of maintaining one's initial impression despite evidence pointing to the contrary. Here, we interpreted newer information (i.e. undetectable copper) from the reference point of our anchor (i.e. multiple myeloma), instead of seeing it objectively.
- In our case, the final diagnosis of copper deficiency was only made during noon report. While clinical reasoning errors due to cognitive biases are sometimes unavoidable, this case highlights the importance of second opinions and feedback. By providing and receiving constructive feedback during sign-out, cross-coverage, and noon report, physicians at all stages can work as a team to minimize errors and improve patient care.