CASE REPORT

Unexpected hypozincaemia in a patient with discharging empyema that proved resistant to replacement therapy

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SUMMARY

A 45-year-old man was admitted with a massive discharging empyema. He had severe chronic malnutrition and was noted to be zinc and selenium deficient. A high-calorie oral diet supplemented with iron, zinc and selenium was started, together with antibiotic therapy and continued prescription of the patient's regular medication, including a PPI (proton pump inhibitor). Although selenium increased to normal levels after 4 weeks of supplementation, zinc levels failed to normalise. Antibiotic therapy improved the empyema and a steady increase in weight was achieved. The patient was noted to have erythematous skin lesions, hair loss and reduced wound healing, all of which may be attributable to zinc deficiency. We propose that competition for intestinal absorption of nutrients and the use of a PPI may have covertly contributed to the inability to normalise serum zinc levels in this case.

BACKGROUND

Trace nutrient deficiencies may often be insidious and go unrecognised in acute or chronic illness. This case report represents a case of hypozincaemia that was surprisingly resistant to replacement therapy.

Only on further investigation did we discover that the multiple nutritional supplements, PPI and antibiotic therapy administered could impede the zinc replacement and that chronic hypozincaemia may have predisposed the patient to alcohol-induced lung injury and contributed to the delayed recovery from infection.

Zinc is an essential dietary element and is not stored as such in the body. However it is found widely in skin, hair, teeth, bone, liver, muscle, leucocytes and testes.

CASE PRESENTATION

A 45-year-old, white British man with a history of alcohol and drug use was transferred from a tertiary respiratory centre to our respiratory unit with a persistently discharging, loculated empyema (figure 1). Five weeks earlier, the patient had undergone thoracotomy for debridement and decortication for his empyema after having received multiple prolonged courses of antibiotics (including co-amoxiclav), with poor response. Cultures from drained pus consistently grew *Klebsiella pneumoniae*. On admission the patient was noted to have chronic malnutrition, and had lost 12 kg (21% of his body weight) since the last admission (56–44 kg

recorded). At this time it was difficult to tell if the poor nutrition was responsible for the infection or vice versa.

INVESTIGATIONS

Owing to chronic malnutrition the team measured trace elements and the patient was found to be profoundly hypozincaemic. He was also selenium deficient, had a raised serum copper and continued to have high levels of inflammatory markers. Low serum zinc may have been due to low serum albumin, since 80% of zinc is bound to albumin. However, zinc is also rapidly transferred to the intracellular compartment from albumin at the start of the systemic inflammatory response so the bio-available zinc may still have been normal.

DIFFERENTIAL DIAGNOSIS

He was diagnosed with a discharging empyema following complicated pneumonia on a background of chronic malnutrition and newly diagnosed trace element deficiencies.

TREATMENT

He was started on an oral, high calorie (3000 kcal/day) and protein (80–100 g/day) diet but after approximately 12 days, due to the poor response, he was started on nasogastric (NG) feeding in addition to an oral dietary intake. Six days into NG feeding (day 18), selenium (100 µg once daily Selenase), zinc (125 mg three times daily Solvazinc) and magnesium (Magnaspartate once daily) supplements were introduced. Other regular medications were continued including lansoprazole (30 mg once daily) and ferrous sulfate (200 mg three times daily). Iron was prescribed prior to admission following a gradual fall in haemoglobin, to a level of 8.5 g/dl, with associated symptoms of tiredness (difficulty mobilising) and lethargy. After 10 days of NG feeding the patient's weight remained at 44 kg so increased calorie intake (4500 kcal/day) was prescribed (day 21). The patient was not considered to be at risk of refeeding because despite having a low body mass index he had always had a reasonable calorie intake. He had never gone through a period of starvation and it was a surprise to the dieticians for him not to gain weight on such a high-calorie diet. Ultimately, this was thought to be due to his severe catabolic state and high-energy needs due to his infection. Serum phosphate was never below 0.83 mmol/l and potassium was never below 3.4 mmol/l. Occasionally, there were problems encountered with the NG tube becoming blocked or dislodged and

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Figure 1 X-ray of empyema prethoracotomy and post-thoracotomy.

requiring re-insertion (indicated by arrows on kcal and weight plot in figure 2). After an initial suboptimal response to co-amoxiclav, antibiotics were withheld (day 15) so that GI side effects would not undermine weight gain or worsen malnutrition-related immunocompromise. A prolonged course (4/52) of Ciprofloxacin was then started after 12 days of NG feeding (day 23).

OUTCOME AND FOLLOW-UP

During his admission the selenium levels steadily increased and normalised (figure 2). Serum zinc levels however, remained low despite an increase in albumin. Magnesium increased initially but then dropped slightly and remained below the reference range. One month after admission to the respiratory unit he was reviewed in clinic for a postsurgical follow-up who advised

continuation with the current treatment and noted that the chest drain bag continued to produce large volumes of pus (60–80 ml on that particular day). Two weeks later he was discharged to a local drug and alcohol rehabilitation unit, was subsequently prematurely discharged and was readmitted 2 weeks later to the respiratory unit with worsening weakness and falls. Zinc and selenium levels were measured at this time and were again in the deficient range. During this admission, the visible signs and symptoms of zinc deficiency first became evident and included hair loss, erythema and poor wound healing. Before further treatment could recommence, the patient absconded from the ward multiple times and returned intoxicated. He was then discharged from hospital with a plan to follow-up as an outpatient in 2 months time.

Figure 2 Graphs of biochemical results for Cu, Zn, Se, Mg, albumin, CRP, Fe and Hb with calorie supplements and weight recorded during admission. Blue dotted line denotes NG feeding commenced; pink line denotes zinc and selenium supplementation commenced; grey dotted line denotes ciprofloxacin introduced; shaded blue areas denotes normal reference intervals.

DISCUSSION

Plasma/serum zinc, iron and selenium are often low in the systemic inflammatory response (SIR). In the case of iron, the response is believed to be a host-defence mechanism in order to reduce the availability of iron to pathogens, involving upregulation of hepcidin which inhibits iron release from macrophages and absorption from the gut, in addition to the production of lactoferrin from inflammatory neutrophils which bind iron thus removing it from the bioavailable pool. Low zinc is believed to be due to an increased requirement for zinc in the liver for hepatic synthesis of acute phase proteins and/or the redistribution into tissues. Plasma/serum zinc levels provide only a crude estimate of zinc status of a patient and do not reflect the intracellular or tissue concentrations, especially in SIRS. Low plasma/serum zinc occurs due to increased uptake into cells in order to meet the additional requirements during SIRS. Low selenium may also be due to increased utilisation (ie, the upregulated synthesis of the antioxidant glutathione peroxidase in order to combat increased oxidative stress) or due to redistribution of selenoprotein P (Se transport protein) in a manner similar to that of albumin as a negative acute phase reactant.¹ In the case presented here, serum selenium increased as the C reactive protein level decreased, whereas zinc levels failed to increase during the same time. Also the albumin level steadily increased during this time and so suggested a continuing process of zinc cellular uptake and/or loss.

We retrospectively reviewed the patient's notes together with the biochemical data and performed literature searches in order to investigate reasons for the persistently low zinc levels despite seemingly adequate replacement in this patient. To our knowledge, there have been no similar cases of treatment-resistant hypozinaemia associated with empyema reported in the literature.

Extraintestinal losses of zinc via excretion in urine and pus² were considered but when calculated were deemed negligible in comparison to the amount being supplemented.

Solvazinc administered as 125 mg contains 45 mg elemental zinc. Therefore our patient was receiving 135 mg elemental zinc per day. Urinary zinc measured on a random sample was 11.76 µmol/l (estimated losses = $11.76 \mu\text{mol/l} \times 2 \text{ l urine/day} \times {}^{65}\text{Zn} = 1.5 \text{ mg/day}$). Zinc potentially lost in the large amount of pus produced per day was also insignificant (zinc in pus @ $2.5\text{--}4.2 \times (\text{ULN serum} = 25 \mu\text{mol/l}) \times 60\text{--}80 \text{ ml pus} \times {}^{65}\text{Zn} = 244\text{--}546 \mu\text{g/day}$).

We identified multiple factors in this case that may have been important in contributing to persistent hypozinaemia:

1. Iron inhibits zinc absorption in a rat model,³ so co-administration of both these elements may result in competition for intestinal absorption.
2. Antibiotic therapy can inhibit intestinal absorption of nutrients, including zinc.⁴
3. HCl (hydrochloric acid) in the stomach aids in the release of metal ions for absorption⁵ and so the use of a proton pump inhibitor, together with occasional vomiting in this patient may have reduced the stomach acid and hence reduced the zinc (and magnesium) available for absorption.
4. During the acute phase response to infection, circulating zinc may be low due to increased utilisation for the synthesis of acute phase proteins, control of reactive oxygen species, regulation of gluconeogenesis and control of microbial growth.⁶

Our patient was probably hypozinaemic for a long period of time and the signs of zinc deficiency were first documented

2 months after serum zinc was first noted to be low. We were cautious not to label our patient as zinc deficient too early since it is often difficult to interpret serum/plasma zinc levels in such a patient, particularly during the SIR, but this patient did eventually develop clinical zinc deficiency. However, our main conclusion is that zinc replacement failed to increase serum zinc levels mainly because of failure of intestinal absorption which was due to co-administered medication in this patient. Parenteral zinc supplementation was not pursued in this patient due to the risk of infection and perhaps due to lack of understanding the true importance and relevance of zinc in the context of this patient's chronic infection. However, in view of the problems encountered with competition for absorption, intravenous zinc may have been helpful in this patient, in improving immune function and wound healing and in preventing the signs of clinical zinc deficiency, and should be seriously considered in future similar cases.

Learning points

- ▶ Trace nutrients are essential for normal immune function.
- ▶ Deficiencies are particularly associated with chronic malnutrition and can present insidiously and remain undiagnosed if not investigated.
- ▶ Zinc deficiency may occur with excess alcohol and be associated with complications of pneumonia,⁷ poor treatment response and prolonged recovery via poor wound healing and tissue repair.
- ▶ Trace elements can be easily supplemented in the diet or if necessary by NG/intravenous administration. When co-administering multiple ions and supplements, potential interactions or competition for absorption and trace element losses should be considered to optimise replacement therapy.
- ▶ Critically, low plasma zinc is not necessarily indicative of zinc deficiency. This is because adequate amounts of bioavailable zinc may still be present after zinc is released from albumin in the plasma and transferred into the intracellular compartment within the liver and other tissues to support protein synthesis. Thus, there is an important distinction between hypozinaemia and zinc deficiency.

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