CASE REPORT

Nutmeg Liver Secondary to Congestive Cardiac Failure Associated with an Elevated CA 19-9 and Hypercalcaemia: a Case Report.

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Abstract

Nutmeg liver describes the radiological appearance of hepatic congestion, characterised by mottled heterogeneous parenchymal enhancement on a contrast-enhanced CT scan, resembling the cut surface appearance of a nutmeg. Carbohydrate antigen 19-9 (CA 19-9) is a glycoprotein tumour marker clinically associated with pancreatic and biliary malignancy. Elevation in CA 19-9 is not widely recognised to be associated with a nutmeg liver. We report a case of a 57-year-old man with systolic cardiac insufficiency causing secondary hepatic congestion (nutmeg liver) associated with an elevated CA 19-9 (252.9 U/ml) and severe hypercalcaemia (3.99 mmol/L).
We describe the diagnostic work-up and treatment strategies undertaken in this complex case. We discuss the pathophysiological mechanisms underlying different causes of congestive hepatopathy and correlate them with the subsequent elevation in CA 19-9. CA 19-9 is exclusively excreted in bile. Congestion of the hepatic sinusoidal system physically compresses intervening biliary canaliculi, leading to cholestasis and subsequently an elevated CA 19-9.
We summarise the causes of mild and marked elevations in CA 19-9, covering an array of malignant and non-malignant conditions, acting as a topic primer for further research into this field.

Keywords: *Congestive hepatopathy, Budd-Chiari syndrome, sinusoidal obstruction syndrome, cholestasis, familial hypocalciuric hypercalcaemia, immobility-induced hypercalcaemia.*

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Introduction

Nutmeg liver is a radiological appearance of a volume-congested liver characterised by mottled, heterogeneous pattern of parenchymal contrast enhancement on a contrast-enhanced CT scan. This congestion may be caused by several conditions, including right-sided cardiac failure and obstruction of the hepatic venous-sinusoidal system. There is a paucity of information in the literature associating hepatic congestion with elevations of the tumour marker, CA 19-9. An elevation in CA 19-9 in a context of a nutmeg liver may be bewildering to the treating physician. We report a case of a nutmeg liver associated with an elevated CA 19-9 and hypercalcaemia.

Case report

A 57-year-old Indian man with a background of long-standing type 2 diabetes mellitus and hypertension presented with a rapid-onset bilateral lower limb weakness associated with slurred speech. He presented to the emergency department 2 days later when he was noticed to be increasingly confused. He had an antecedent episode of fever with abdominal cramps, diagnosed as viral acute gastroenteritis 2 weeks prior.

On examination, he was pleasantly confused with a Glasgow Coma Scale of 14/15 and a left lower facial droop. Due to difficulty obeying command, it was difficult to accurately assess his muscle strength, but all his four limbs were moving with an MRC scale of at least 4/5. His deep tendon reflexes were present throughout though his Babinski's reflexes were equivocal bilaterally. His blood pressure was 126/71 mmHg with a regular pulse of 98 beats per minute. No carotid bruits were audible. He was afebrile and his capillary blood glucose was 5.8 mmol/L. The rest of his physical examination was unremarkable, and no evidence of Guillain-Barre syndrome was present clinically.

His electrocardiogram confirmed a normal sinus rhythm with no acute ischaemic changes and a plain CT scan of his brain revealed chronic peri-ventricular small vessel ischaemia with well-defined hypodensities in the left thalamus representing an acute infarct.

Laboratory evaluation revealed a highly elevated serum corrected calcium (Ca^{2+}) of 3.99 mmol/L. His renal profile and other electrolytes revealed a Na^+ 135 mmol/L, K^+ 3.2 mmol/L, creatinine 196 µmol/L, urea 7.8 mmol/L and PO_4^{3-} of 1.13 mmol/L. His serum parathyroid hormone (PTH) was undetectable (< 0.32 pmol/L). His liver function tests revealed mild hyperbilirubinaemia (41 µmol/L), ALT 31 IU/L, elevated ALP (602 IU/L) and reduced albumin (24 g/L). His urine dipstick demonstrated a semi-quantitative proteinuria of 2+. His full blood count revealed a haemoglobin of 15.1 g/dL, leukocyte count 8.9 x 10^9/L, platelets of 315 x 10^9/L. and an erythrocyte sedimentation rate of 42 mm/hour. His thyroid function test was normal.

Based on the above, we have yielded a clinical diagnosis of acute ischaemic stroke with hypercalcaemic crisis, contributing to his delirium. He was commenced on aspirin with atorvastatin for the stroke and 6 pints of normal saline per day to enhance urinary calcium excretion. Concurrent oral and intravenous potassium replacements were also instituted. Subcutaneous salmon calcitonin 250 IU twice daily was added after 24 hours and a single dose of intravenous pamidronate 60mg was given which finally normalised his serum Ca^{2+}. His delirium and weakness resolved with the resolution of hypercalcaemia. Unfortunately, he developed fluid retention secondary to the intravenous saline given to treat his hypercalcaemia, demonstrated by lower limb swelling to his mid-thighs and fine basal crackles upon lung auscultation. Intravenous fluids were then discontinued.

Due to the significant hypercalcaemia with suppressed PTH, a search for malignancy was commissioned. A myeloma screen was negative (skeletal survey normal and no paraprotein was detected on serum and urine electrophoresis). His tumour markers were satisfactory except for an

elevated CA 19-9 which was 252.9 U/ml (normal range 0 to 37 U/ml). His autoimmune liver screen was negative (AMA, anti-SMA, anti-LKM). His serum immunoglobulins did not reveal any evidence of immune-paresis or significant IgG subset abnormalities. A contrast-enhanced CT scan of his thorax-abdomen and pelvis revealed a smoothly outlined liver measuring 16 cm in span with heterogeneous parenchymal liver enhancement (nutmeg liver). There were no suspicious focal hepatic lesions, surface nodularity or capsular enhancement. The hepatic veins were slightly narrowed but patent, with no evidence of thrombosis. There was no biliary dilation, and the pancreas was normal in its entirety (Figure 1a to c). A subsequent echocardiogram revealed diffuse ventricular wall motion hypokinesia and a compensated left ventricular ejection fraction of 45% with no structural valvular abnormalities (functional tricuspid regurgitation).

Since this patient was clinically well, a joint decision was made to defer a liver biopsy to investigate his elevated CA 19-9. He was commenced on perindopril for cardiac remodelling and to reduce proteinuria in addition to fluid restriction. He was not commenced on loop diuretics, mineralocorticoid receptor antagonists or SGLT inhibitors at this stage. Upon follow-up, his monthly serum calcium remained within the high-normal range. Two months later, he has clinically improved with resolution of his peripheral oedema. His chest was clear upon auscultation, and his jugular venous pressure was normal. His cholestasis improved with his ALP reduced to 382 IU/L. The rest of his liver function test revealed a bilirubin of 9.8 µmol/L, ALT 21.9 IU/L and an albumin of 32 g/L. His repeat CA 19-9 taken 4 months later subsequently normalised (36 U/ml). A 24-hour urine collection for electrolyte excretion revealed renal calcium excretion below the detection limit of 0.5 mmol/l (normal range 2.5 to 7.5 mmol/L/day) with a calcium to creatinine clearance ratio of less than 0.01.

Based on these findings, we further reviewed his history. He denied any family history of hypercalcaemia to the best of his knowledge. Review of his past laboratory results during his fever episode revealed a pre-morbid baseline serum calcium of 2.72 mmol/L. This most likely reflects his usual hypercalcaemia which was missed in hindsight. In view of these, the final diagnosis yielded was a nutmeg liver with elevated CA 19-9 secondary to fluid overload (a combination of cardiac insufficiency and hypo-albuminaemia due to diabetic nephropathy). His hypercalcaemia was attributed to a calcium sensing disorder most likely familial hypocalciuric hypercalcaemia (FHH). Genetic studies were not performed as it was not available in our facility.

The patient reported feeling more energetic with increasing capability of performing daily activities following resolution of his hypercalcaemia. He expressed relief that no occult malignancy was found and appreciated the clear explanation provided by the clinical team regarding his complex diagnosis. He remains adherent to his medications and attends all scheduled follow-up appointments. He remains well up to the writing of this manuscript (20-months post-discharge).

Discussion

The case above illustrates a nutmeg liver due to passive hepatic venous congestion secondary to congestive cardiac failure. The fascinating element in this case is the concomitant presence of an unexplained severe hypercalcaemia with a suppressed PTH. This combination has naturally set off a ‘wild goose chase’ in search of an occult malignancy. The search for malignancy was very well justified, compounded by the presence of an elevated CA 19-9 together with a cholestatic pattern of elevated liver enzymes.

From a pathophysiological perspective, right-sided cardiac failure causes elevated hydrostatic pressure in the right atrium, which is transmitted to the vena cava. Since the hepatic veins do not

possess valves, increased pressure in the inferior vena cava is directly transmitted backwards to the hepatic venous system and sinusoids. The engorged and congested hepatic venous system produces the characteristic features of a 'nutmeg liver' on a contrast-enhanced CT scan [1]. Furthermore, congested hepatic sinusoids and peri-sinusoidal oedema will physically compress adjacent hepatocyte plates and the intervening biliary canalicular system, leading to biliary stasis and a cholestatic pattern of elevated transaminases. Causes of a nutmeg liver are characterised in Table 2.

CA 19-9 or sialyl-Lewis-a is a cell surface glycoprotein complex important for epithelial cell signalling [7]. It's produced by epithelial cells lining many organs but predominantly the pancreas and bile ducts. Although CA 19-9 is primarily used in clinical practice as a screening biomarker for pancreatic ductal adenocarcinoma and cholangiocarcinoma, it can also be elevated in other types of malignancy and a wide range of benign conditions. An elevated CA 19-9 is due to excessive production or secretion of the molecule, impairment of excretion, or a combination of the two. Though produced by many different organs, CA 19-9 is exclusively excreted in bile (via the biliary and pancreatic ducts). Hence, any form of biliary obstruction may lead to elevation in serum CA 19-9. There are no consensus guidelines on classifying the degree of elevated serum CA 19-9. Malignancy will generally cause a more marked elevation, often above 1000 U/ml. However, there are exceptions to this rule.

Malignancy of the pancreatic-biliary system, stomach and colon usually causes marked elevation of CA 19-9 but malignancy involving the female reproductive tract often causes CA 19-9 elevation below 1000 U/ml [8]. Similarly, various non-malignant conditions cause CA 19-9 elevation which generally is below 1000 U/ml. These include acute hepatitis, chronic liver disease, pancreatitis, cystic fibrosis, diabetes mellitus, interstitial lung disease (ILD), collagen vascular disease (more likely in patients featuring ILD), endometriosis and Hashimoto's thyroiditis. Peculiar to this rule, non-malignant chronic cholestasis may cause CA 19-9 elevation exceeding 1000 IU/ml [8]. In chronic cholestasis, hepatocytes undergo metaplasia, differentiating into functional cholangiocyte-like cells (ductular reaction) which subsequently produces further CA 19-9. In the presence of pre-existing biliary obstruction, the CA 19-9 elevation increases in magnitude [9].

Our patient had a modest elevation of CA 19-9 as the duration of cholestasis is relatively short and reflects excretory impairment secondary to partial obstruction.

Additional to the hepatic issues discussed above, our patient also presented with severe hypercalcaemia and a suppressed PTH. Extensive workup eventually revealed underlying hypocalciuria as the cause for the hypercalcaemia. The severity of hypercalcaemia was amplified due to a period of immobility, secondary to the stroke that he has suffered. Immobility is well known to rapidly increase osteoclast activity leading to bony resorption (within 48 hours) [10]. Typically, hypercalcaemia from bone resorption is regulated by renal tubules via increasing fractional excretion of calcium to maintain normo-calcaemia. In FHH, the tubular calcium sensing receptor (CaSR) is less sensitive to circulating calcium levels and continues tubular reabsorption of calcium despite serum hypercalcaemia (this mechanism predominates in the loop of Henle and is independent of PTH action in the proximal convoluted tubule). This lack of homeostasis causes the sharp rise in serum calcium, leading to clinical features discussed.

The diagnosis of FHH was not entertained earlier as this condition usually presents with a mildly elevated PTH level. Despite a loss of function mutation of the CaSR gene, patients with FHH possesses functional CaSR protein (but with an attenuated sensitivity). Hence, highly elevated serum calcium will suppress PTH levels once the threshold is reached. In the absence of thiazide diuretics, differentials for the significant hypocalciuria would include FHH, vitamin D

deficiency and Gitelman syndrome. However, with the significant hypercalcaemia, FHH best describe this phenotype. Nevertheless, due to the absence of a positive family history (which is relatively common as patients with this condition are asymptomatic), genetic studies will be required to confirm the diagnosis.

Conclusion

Nutmeg liver is the radiological appearance of hepatic congestion. Hepatic congestion may be due to cardiac failure or obstruction of the hepatic venous-sinusoidal system. Hepatic congestion from any reason will cause impairment of biliary drainage, which will subsequently lead to an elevated CA 19-9. In the absence of malignancy, hepatic congestion and a variety of non-malignant diagnoses are well-established causes for an elevated CA 19-9. Despite this, when faced with a significantly elevated CA 19-9, a good clinico-pathological (including laboratory and imaging studies) assessment by the physician is essential to rule out occult malignancy prior to entertaining the list of benign diagnoses.

Additionally, immobility-induced bony resorption should form the basic differential diagnosis for hypercalcaemia with a suppressed PTH. This is even more important in patients with a pre-existing calcium sensing disorder, as illustrated in our case.

Ethical declaration

Verbal informed consent was obtained from the patient for the publication of this case report and any accompanying images. The patient was assured anonymity of his identity.

Authors' contribution

SIJ followed up the patient in clinic, contributed to the diagnosis and patient management, and prepared the manuscript for submission. BCMK managed the patient in hospital, conducted outpatient follow-up and management, and reviewed the manuscript prior to submission. ZMY prepared and reported the computerised radiological images and reviewed the manuscript before submission.

Declaration of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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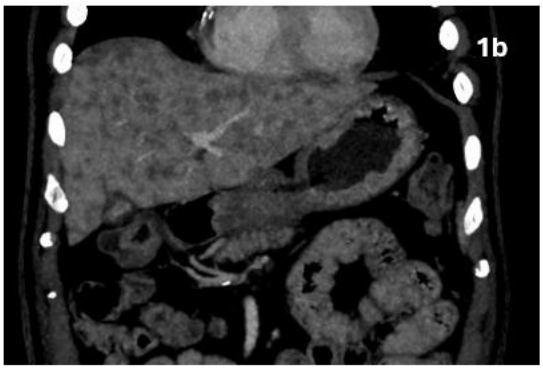
Time point	Event
Day minus 14	Presented to the emergency department (ED) with fever and abdominal cramps; diagnosed with viral gastroenteritis, and was discharged with supportive treatment.
Day 0	Developed acute onset paraparesis with dysarthria, with reduced mobility (bed-bound).
Day 2	Brought to the ED with delirium (confusion and behavioural changes). Severe hypercalcaemia with a suppressed PTH was noted. Intravenous saline were commenced alongside treatment of acute ischaemic stroke.
Day 3	Subcutaneous salmon calcitonin twice daily and a single dose of intravenous pamidronate 60mg were given due to persistent hypercalcaemia. Elevated serum CA 19-9 was noted.
Day 4	Delirium resolved and improvement in lower limb weakness alongside steadily decreasing hypercalcaemia.
Day 5	Hypercalcaemia resolved. Salmon calcitonin was discontinued.
Day 7	Clinically in volume overload. Intravenous saline was discontinued.
Day 9	Serum calcium remained normal, and pulmonary congestion resolved. Discharged from hospital.
Day 42 (week 6)	Contrast-enhanced CT scan revealed a nutmeg liver.
Week 10	Clinic review with analysis of imaging and laboratory work-up: Provisional diagnosis of nutmeg liver secondary to cardiac failure was made. Fluid restriction and perindopril commenced.
Week 19	Clinic review with further analysis: Clinically euvolaemic with improvement in liver function tests. Echocardiogram confirmed systolic cardiac failure.
Week 37	Remained well. Calcium-to-creatinine clearance ratio discovered to be less than 0.01. Repeat CA 19-9 had normalised. Full diagnosis of nutmeg liver secondary to congestive cardiac failure and familial hypocalciuric hypercalcaemia made.
Week 82	Final follow-up. Patient remained well with no recurrence of hypercalcaemia or deranged liver function.

Table 1. Simplified clinical event timeline.

Table 2. Causes of a nutmeg liver (congestive hepatopathy)

Aetiology	Pathophysiology	Clinical associations
1. Extrahepatic		
▪ Cardiac failure	Resistance to hepatic venous outflow from passive backlog of intra-cardiac pressure.	Cardiomyopathy, pericardial diseases.
▪ Congenital IVC web		Membranous sheet of elastic fibres without inflammatory cells or fibrosis causing luminal stenosis. Commoner in Japan, India and South Africa [2].
▪ IVC thrombus (also classified under BCS)		Commoner among patients with IVC anomalies and thrombophilia. Less commonly due to extrinsic compression and IVC filter thrombosis [3].
2. Hepatic vein occlusion (BCS)		
▪ Hepatic vein thrombosis	Intra-luminal thrombosis causing venous outflow obstruction.	Thrombophilia, drugs, MPN, PNH, Behcet's disease [4].
▪ Extrinsic compression	Luminal stenosis from external compression, resulting in venous outflow obstruction. Also known as secondary BCS.	Hepatic abscess, cysts or tumours.
3. Sinusoidal obstruction syndrome (SOS)	Sloughing of dead endothelial cells into the sinusoid causing sinusoidal flow obstruction.	Sinusoidal endothelial cell cytotoxicity primarily due to conditioning chemotherapy for haematopoietic stem cell transplantation. Drugs with the highest association include thioguanine, busulfan and oxaliplatin*[5].

*Note that oxaliplatin is also widely used in the treatment of colorectal cancer (CRC). Indeed, increased incidence of SOS is noted in CRC patients with liver metastases [6]. Abbreviations: IVC (inferior vena cava), BCS (Budd-Chiari syndrome), MPN (myeloproliferative neoplasms), PNH (paroxysmal nocturnal haemoglobinuria), CRC (colorectal carcinoma)



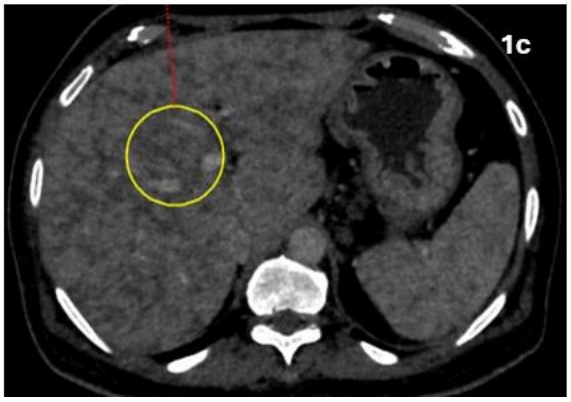


Figure 1a: Axial view of the contrast-enhanced CT abdomen. It demonstrates mottled heterogeneous parenchymal enhancement in the portal venous phase, subsequently becoming uniform on delayed phase (likened to a cut nutmeg).

Figure 1b: Coronal view of the nutmeg liver. Note the presence of a globular cardiomegaly.

Figure 1c: Axial view of the liver in the portal venous phase demonstrating a rim of peri-portal oedema (within the yellow circle). This is a common accompanying feature in hepatic congestion.

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