Author/s:
Sinclair, M;Schelleman, A;Sandhu, D;Angus, PW

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Regression of hepatocellular adenomas and systemic inflammatory syndrome after cessation of estrogen therapy

Marie Sinclair[1,3], Anthony Schelleman[1,2], Daljean Sandhu[1], Peter W Angus[1,3]

1. Austin Health, Gastroenterology and Hepatology
2. Austin Health, Interventional Radiology
3. The University of Melbourne

Corresponding author: Marie Sinclair. Gastroenterology and Hepatology, Austin Hospital, 145 Studley Rd, Heidelberg, Victoria, Australia, 3084. pH : +61394965353. Fax : +61394963487

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Abbreviations: OCP (oral contraceptive pill), ESR (erythrocyte sedimentation rate), CRP (C-reactive protein), ALP (alkaline phosphatase), MRI (magnetic resonance imaging), PET (positron emission tomography), pANCA (p-antinuclear cytoplasmic antibody)

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Summary

We report a case of dramatic systemic inflammatory symptoms and biochemical signs of inflammatory related to multiple hepatic adenomas that completely resolved after cessation of the oral contraceptive pill and associated adenoma regression. This represents the first case of such dramatic symptoms to resolve after estrogen withdrawal alone.

A 43 year-old woman presented with generalised abdominal discomfort, debilitating fatigue, malaise and intermittent night sweats, in conjunction with arthralgia of both small and large joints. She had a past history of obesity and gastric stapling and was prescribed esomeprazole and the oral contraceptive pill (OCP). Clinical examination revealed mild right upper quadrant tenderness and a body mass index of 36kg/m^2. There was no fever, rash, synovitis or palpable lymphadenopathy.

On initial investigations, erythrocyte sedimentation rate (ESR) was elevated at 100mm/hour, as was C-reactive protein (CRP) at 45mg/L. Serum albumin was low at 30g/L, and alkaline phosphatase (ALP) elevated at 320 U/L. Liver ultrasound showed hepatic steatosis in conjunction with multiple liver lesions, the largest of which was 8.5cm in diameter. Magnetic resonance imaging (MRI) demonstrated multiple arterially enhancing liver lesions most consistent with hepatic adenomas (Figure 1). Biopsy was not performed due to the characteristic imaging appearance.

Given the severity of systemic symptoms and elevated inflammatory markers, concerns were raised about the possibility of connective tissue disease or occult malignancy. Extensive investigations were performed, including serum vasculitic and tumour markers, positron-emission tomography (PET), nuclear medicine bone scan and serum protein electrophoresis. Other than a mildly positive p-antinuclear cytoplasmic antibody (pANCA) and microalbuminuria with preserved renal function, the remaining investigations were unremarkable.

A diagnosis of adenoma-driven systemic inflammation was considered and therefore the OCP was ceased and lifestyle interventions recommended to induce weight loss. Subsequent imaging revealed a steady decrease in size of the hepatic adenomas and a progressive decline of the inflammatory markers. Almost four years after ceasing the OCP, systemic symptoms and microalbuminuria resolved, inflammatory markers normalised, and serum albumin rose to 35g/L. At this time, arterial enhancement of all lesions was markedly reduced and the largest adenoma had shrunk from 8.5 to 4.2cm in diameter (Figure 2).

Discussion

This case illustrates a rare but recognised manifestation of hepatic adenoma. The initial symptoms raised concerns about the possibility of significant systemic disease. Although histopathology was not available, the probability that the syndrome was due to estrogen-dependent hepatic adenomas was strongly supported by shrinkage of the tumours, resolution of symptoms and normalisation of inflammatory markers following cessation of the OCP.

Inflammatory hepatocellular adenomas (HA-I) comprise 30-50% of all hepatic adenomas and are characterised by intra-lesional inflammatory infiltration and increased amyloid-A and C-reactive protein expression. Hepatocyte nuclear factor 1A-inactivated subtype (HA-H) comprises 35-40% of adenomas, and tends to have intra-tumour steatosis related to increased lipogenesis. The beta catenin-mutated subtype (HA-B) comprises 15% of adenomas, and is associated with progression to hepatocellular carcinoma (1). In our patient, MRI imaging was strongly suggestive of hepatic adenomas, with characteristic features including arterial phase enhancement without portal venous washout, and reduced signal intensity on hepatobiliary phase scans. The finding of diffuse hepatic steatosis in the surrounding non-tumour liver suggested the subtype was HA-I, since such steatosis is rare in association with other adenoma subtypes (2).

Systemic symptoms have been described in patients with inflammatory adenomas, however the syndrome appears to be rare. Previous case studies report systemic inflammatory presentations in young women with single large liver lesions that were confirmed to be the HA-I subtype after resection (3, 4). The rapid resolution of symptoms post-operatively strongly suggested the adenoma was solely responsible for their illness. Systemic reactive amyloidosis with associated nephrotic syndrome has also been shown to resolve following resection of an adenoma (5). In our patient, resection was precluded by the presence of multiple liver lesions, all of which had similar MRI appearance. This is the first report to our knowledge of complete resolution of a severe hepatic adenoma-induced systemic inflammatory syndrome after cessation of estrogen therapy.

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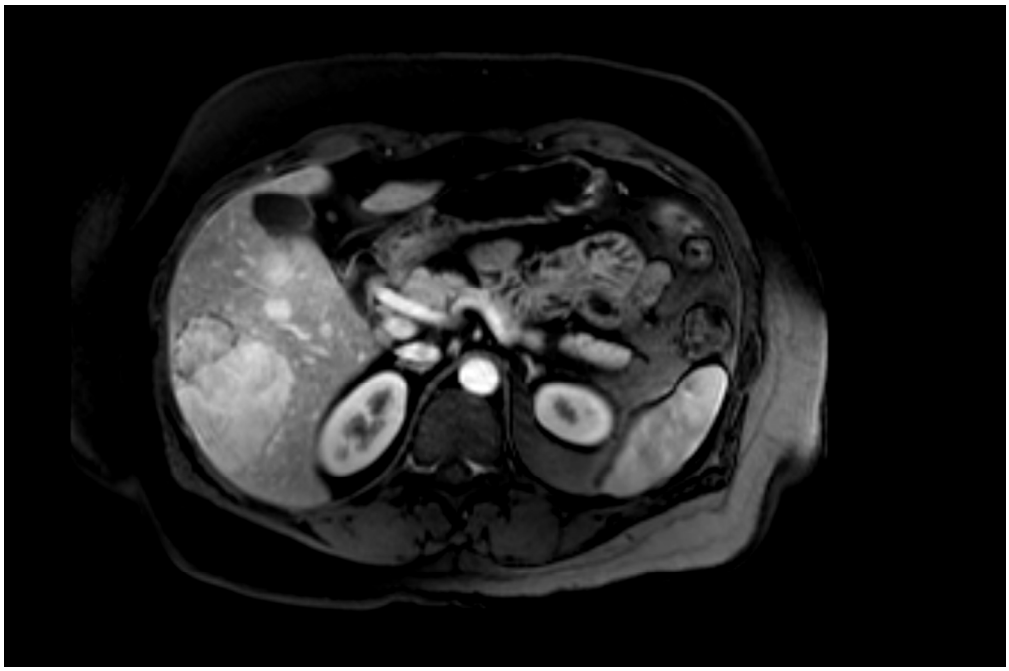
Figure 1. Original imaging at diagnosis prior to OCP withdrawal

Arterial phase post contrast axial T1 weighted image demonstrates an 8.5 cm lesion in segment 6 laterally, with moderate, heterogeneous and diffuse arterial phase contrast enhancement. Multiple other lesions with similar imaging characteristics were seen in both lobes of the liver.

Figure 2. Four year follow-up imaging, after OCP withdrawal

Arterial phase post contrast axial T1 weighted image, demonstrating reduction in size and degree of arterial phase enhancement within the segment 6 lesion



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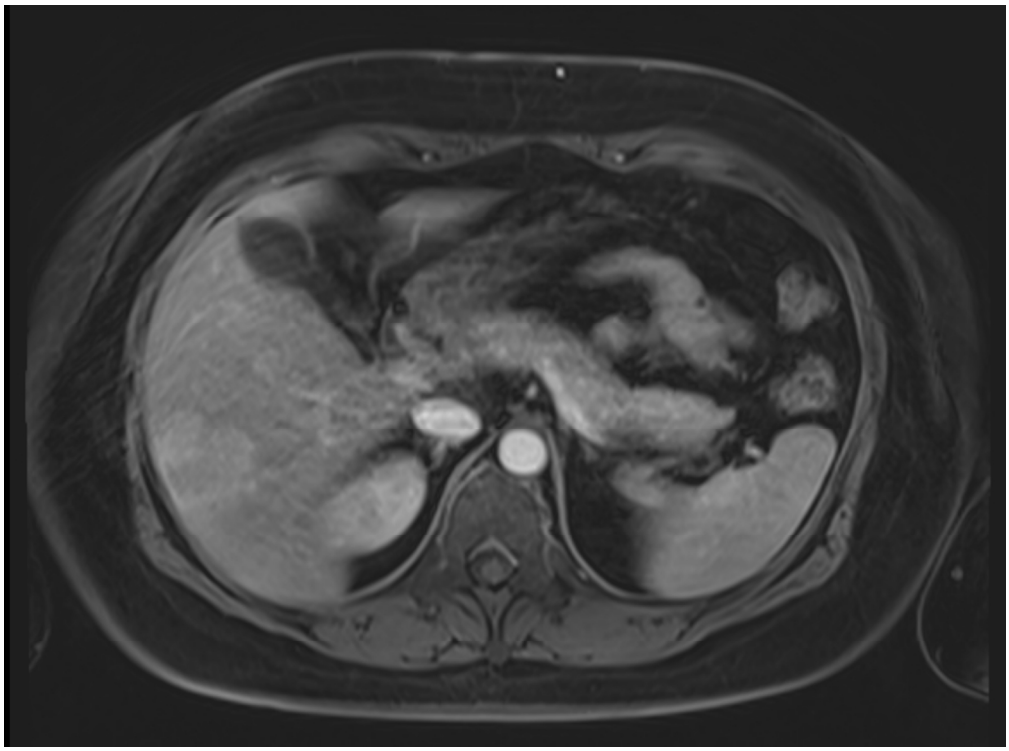

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