resection was carried out. Postoperative course was uneventful, and the one year follow-up was normal. Macroscopically the tumour was 12 × 10 × 5 cm, well-demarcated from the darker normal hepatic parenchyma and unencapsulated. The tumour showed microscopical features consistent with liver cell adenoma (LCA): bland hepatocytes arranged in irregular cell cords, two or three cells thick, that were separated by sinusoids; and also absence of fibrosis and proliferating bile ducts, which excludes the possibility of focal nodular hyperplasia of the liver (FNH).

Large symptomatic hepatic haemangiomas and liver cell adenomas, are rarely seen.[2,3] Recent evidence indicates that LCA is associated with the use of oestrogenic hormones.[4,5] On the other hand, FNH is considered to be of developmental origin like haemangioma. It has been reported that, in women, gonadal contraceptives and steroids may exert a trophic effect on preexisting focal hyperplasia to gradually transform to liver cell adenoma.[5] Our adenoma case had a history of the irregular use of long acting progesterone, which is a not uncommon practice for birth control purposes in the rural areas of the South Pacific islands.

We believe that the lesion in Case 2 may have started as FNH and gradually transferred to LCA with progesterone. This seems likely because her sister had haemangioma, also a developmental lesion of the liver. The second possibility is that the patient had LCA, and that the use of progesterone contributed to the growth of the lesion. On the other hand, it is not possible to comment as to why the haemangioma reached such an unusual size. Clinical screening of other members of the family of our patients was not carried out, but family history revealed no additional information.

Acknowledgements

This study was carried out during the author's assignment to Western Samoa as pathologist under UNV/UNDP project between 1986–88. The author thanks Drs S. McCarthy and J. Painter from the Pathology Department of the Royal Prince Alfred Hospital, Sydney, Australia for their help.

Nadir Paksoy
Department of Pathology,
School of Medicine,
c/o PK: 351, 0700 Antalya, Turkey.

References

1. Karhunen, P.J. Benign hepatic tumours and tumour like conditions in men. *J Clin Pathol* 1986, **39:** 183–188.
2. Adam, Y.G., Huvos, A.G. & Fortner, J.G. Giant hemangiomas of the liver. *Ann Surg* 1970, **172:** 239–245.
3. Gold, J.H., Guzman, I.J. & Rosai, J. Benign tumors of the liver. *Am J Clin Pathol* 1978, **70:** 6–17.
4. Karhunen, P.J. *Benign Tumors, Tumor-Like Conditions and Preneoplastic Lesions of the Adult Human Liver.* Academic dissertation, Department of Forensic Medicine, University of Helsinki. 1986, pp. 10–67.
5. Ishak, K.G. The Liver. In: Ridell, R.H. (ed.) *Pathology of Drug-Induced and Toxic Diseases.* Churchill Livingstone, New York, 1982, pp. 427–513.

Myelofibrosis with bleeding jejunoileal angiodysplasia diagnosed by intraoperative endoscopy

Sir,

Massive haemorrhage from diffuse angiodysplasia (AD) of the jejunum and ileum is a rare condition which may be difficult to diagnose. We describe a patient with myelofibrosis and recurrent melaena due to jejunoileal angiodysplasia where the diagnosis was made by intraoperative endoscopy (IOE).

A 73 year old male, known to have myelofibrosis, was admitted to the Rambam Medical Center with melaena. The haemoglobin level was 5.1 g/dl and platelet count 20,000 per litre. Prothrombin time and partial thromboplastin time were normal. Blood transfusions were given. Upper and lower gastrointestinal tract barium series and endoscopy did not show any pathology and the patient was discharged. A few days later the patient was readmitted because of syncope, melaena and a haemoglobin level of 4.6 g/10 ml. Radioisotopic examination failed to show Meckel's diverticulum. Enteroclysis and repeated upper and lower endoscopy were normal. A week later, the melaena recurred. Scanning with technetium 99-labelled autologous red blood cells suggested the presence of active bleeding in the regions of the ascending colon, right and left flexures. However, coeliac angiography following this scanning was normal.

After 4 weeks of continuous bleeding, that required a transfusion of 65 pints of blood to keep the haemoglobin stable, an exploratory laparotomy was performed. Intraoperatively, a colonoscope was introduced through the mouth, and passed to the small intestine. The scope was passed along the small intestine by invaginating the intestine over the colonoscope. The IOE with transillumination disclosed multiple jejunoileal angiodysplastic lesions. Some of the lesions were actively bleeding and were sutured. Histological examination of the biopsy from one of such lesions confirmed the endoscopic diagnosis of AD. A week later the patient died from massive gastrointestinal bleeding.

Angiodysplasia (a focal submucosal vascular ectasia) of the bowel is an uncommon source of massive gastrointestinal bleeding. The majority of cases occurring in the right colon in elderly patients. Jejunoileal AD is more rare[1–3] and has a high rate of recurrent bleeding, presumably from the multiplicity and multifocality of lesions. Bleeding jejunoileal AD is difficult to diagnose by an invasive procedure such as endoscopy or contrast angiography because haemorrhage is unexpected with a slow rate of bleeding and the source is the 'blind area' of the gastrointestinal endoscopy. Occasionally even exploratory laparotomy may fail to diagnose jejunoileal AD. In such cases, OIE enhances the surgeon's ability to find the bleeding lesions.[4,5] Increased awareness and exploratory laparotomy with IOE may allow more frequent recognition of jejunoileal AD. Because small intestinal AD may sometimes by localized and treatable by segmental resection, a careful use of this procedure is recommended.

Yeouda Edoute[1]
Nadim Farrag[1]
Hedviga Kerner[2]
Dan Duek[3]
Alain Suissa[4]
Jonathan Kaplan[1]
Departments of [1]Internal Medicine C, [2]Pathology, [3]Surgery A and [4]Gastrointestinal Unit, Rambam Medical Center and the Faculty of Medicine, Technion, Haifa, Israel.

References

1. Duray, P.H., Marcal, J.M. Jr, LiVolsi, V.A., Fisher, R., Scholhamer, C. & Brand, M.H. Small intestinal angiodysplasia in the elderly. *J Clin Gastroenterol* 1984, **6:** 311–319.
2. Clouse, R.E., Costigan, D.J., Mills, B.A. & Zuckerman, G.R. Angiodysplasia as a cause of upper gastrointestinal bleeding. *Arch Intern Med* 1985, **145:** 458–461.
3. Vu, H., Adams, C.Z. Jr & Hoover, E.L. Jejunal angiodysplasia presenting as acute lower gastrointestinal bleeding. *Am Surg* 1990, **56:** 302–304.
4. Scott, S.A. & Royle, G.T. Angiodysplasia of the small bowel; a 'brilliant' technique for localizing the quiescent lesion. *Postgrad Med J* 1987, **63:** 995–997.
5. Apelgren, K.N., Vargish, T. & Al-Kawas, F. Principles of use of intraoperative enteroscopy for hemorrhage from the small bowel. *Am Surg* 1988, **54:** 85–88.

Vasculitis due to metolazone

Sir,

A 65 year old man had severe cardiac failure following a myocardial infarction 2 years previously. He had subsequently suffered 2 episodes of haemolytic anaemia, apparently due to captopril and then to lisinopril. In September 1990 he developed an acute, widespread, small vessel cutaneous vasculitis which increased over the next 2 weeks. Four weeks before the onset of vasculitis, his oral medication had been changed from bumetanide and spironolactone to frusemide with amiloride (Frumil®) and isosorbide mononitrate; after 2 weeks the Frumil had been discontinued, frusemide 120 mg daily substituted, and metolazone (Metenix®) 5 mg twice daily had been commenced. The patient had previously taken frusemide without any adverse effect.

On admission to hospital he had extensive vasculitis, without frank necrosis or ulceration, and asymptomatic haematuria. Metolazone was stopped, and the vasculitis resolved within 5 days. No steroid therapy was required, and none of the other medication was stopped; his frusemide dose was actually increased during the following weeks without recurrence of vasculitis. Skin biopsy confirmed a leukocytoclastic vasculitis, mainly affecting small venules; direct immunofluorescence of the biopsy showed deposition of IgG, IgA, IgM and complement C3 in vessel walls. Despite intensive treatment, the patient died a few weeks later; his intolerance of several potentially useful agents limited the therapeutic options.

Although a bullous eruption is more frequent, vasculitis due to frusemide has been documented[1] and is probably better recognized by dermatologists than the small number of cases reported to the CSM would suggest (23 cases recorded; Committee on Safety of Medicines – personal communication). Both frusemide and thiazides are listed as drugs which may cause vasculitis in a monograph on cutaneous effects of drugs.[2] The only previous report of vasculitis received by the manufacturers of Metenix was thought to be due to comcomitant frusemide therapy, but in our patient the timing of changes of medication and the rapid resolution after stopping the drug strongly suggested that metolazone rather than frusemide was the cause of the vasculitis. The occurrence of skin and renal vasculitis due to thiazides has been previously reported in a patient who developed vasculitis related to both hydrochlorothiazide and chlorthalidone, confirmed by rechallenge.[3] The CSM has received two reports of vasculitis in patients taking metolazone, and other rashes reported to the manufacturers or to the CSM include purpura, 'erythema multiforme' and epidermal necrolysis, photosensitivity, and pruritus.

The potential difficulties in management of drug eruptions in patients with severe conditions, and taking multiple essential drugs of which two or more can cause the same pattern of eruption, is well demonstrated by this case. The presence of severe cardiac failure precluded discontinuing both diuretics, yet the rapidly increasing extent of vasculitis in an already severely ill patient required prompt intervention; institution of oral steroid therapy was considered but with reluctance because of the potential for further fluid retention. The timing of the eruption, and the previous uneventful exposure to frusemide, suggested that metolazone was the more likely cause of vasculitis and this was confirmed by the rapid improvement after it was withdrawn; rechallenge was not considered. Cutaneous reactions to diuretics are not rare in dermatological practice but this patient was unusual in having adverse reactions to a number of potentially useful drugs used in treatment of severe cardiac failure.

Acknowledgement

We are grateful to the CSM and to Hoechst UK Ltd for permission to cite their data.

Neil H. Cox
Peter Hodkin
Department of Dermatology, Cumberland Infirmary, Carlisle, CA2 7HY, UK.

References

1. Hendricks, W.M. & Ader, R.S. Furosemide-induced cutaneous necrotizing vasculitis. *Arch Dermatol* 1977, **113:** 375.
2. Bork, K. *Cutaneous Side Effects of Drugs.* W.B. Saunders, Philadelphia, 1988, p. 155.
3. Bjornberg, A. & Gisslen, H. Thiazides: a cause of necrotizing vasculitis? *Lancet* 1965, **ii:** 982–983.