

## ORIGINAL ARTICLE

## Hepatic myspherulosis complicating portal vein embolisation

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**Aims:** Myspherulosis is a rare condition characterised by sac-like structures containing spheroid bodies in cysts or cystic spaces in the tissue. This condition has not previously been reported in the liver. The association with previous portal vein embolisation using a mixture of butyl 2-cyanoacrylate and ethiodised oil and the proposed mechanism of pathogenesis are discussed.

**Methods:** Samples from 8 patients treated by hepatectomy after portal vein embolisation using a mixture of butyl 2-cyanoacrylate and ethiodised oil were retrieved from the archives of the United Christian Hospital, Hong Kong. The histological specimens were reviewed. A panel of histochemical and immunohistochemical stains was used.

**Results:** All cases showed hepatic myspherulosis within the veins. The veins were denuded of endothelium, which was replaced by granulation tissue and fibrous tissue with a lymphoplasmacytic infiltrate. Foreign body-type giant cells (six cases) and eosinophilic infiltrates (seven cases) were noted in most cases. Both parent bodies and endobodies were stained red by Papanicolaou and Masson's trichrome and stained blue by solochrome cyanine. The endobodies showed immunoreactivity towards glycophorin A. They were negative for Alcian blue, periodic acid Schiff, Grocott, and Ziehl-Neelsen stains.

**Conclusions:** The endobodies of myspherulosis may be misdiagnosed as fungi or algae by the unwary. The clinical history, intravascular location, lack of staining with periodic acid Schiff and Grocott stains, and positive glycophorin A staining are generally sufficient for a confident diagnosis of myspherulosis.

Myspherulosis is characterised by microscopic sac-like structures containing spheroid bodies in the tissue. It is infrequently reported in the literature, and its nature was a matter of debate until its pathogenesis was confirmed to be the alteration of red cells by lipid material.

"Portal vein embolisation results in a significantly greater increase in liver volume and a shorter hospital stay than is seen in patients treated by portal vein ligation"

Portal vein embolisation (PVE) is a safe method that is used to increase the functional liver remnant volume and achieve resectability for bulky liver tumours. It is usually indicated when the future liver remnant (FLR) volume is estimated to be too small for major liver resection. A previous study has shown that the hypertrophy of the FLR induced by PVE in patients with chronic liver disease significantly decreased the rate of postoperative complications.<sup>1</sup> In addition, PVE results in a significantly greater increase in liver volume and a shorter hospital stay than is seen in patients treated by portal vein ligation.<sup>2</sup>

To the best of our knowledge, this is the first reported study of myspherulosis in the liver associated with PVE.

## METHODS

A total of eight cases of hepatectomy after PVE were retrieved from the archives of the United Christian Hospital, Hong Kong over a period of two years. Clinical data and follow up information were obtained from the medical files. The histological materials were reviewed, and representative areas were selected for histochemical staining (Papanicolaou, Masson's trichrome, Alcian blue, periodic acid Schiff, Grocott, Ziehl-Neelsen, and solochrome cyanine) and immunohistochemical staining for red blood cells

(glycophorin A; monoclonal antibody JC159; dilution 1/30; Dakopatts, Glostrup, Denmark).

## RESULTS

## Clinical features

Table 1 summarises the clinical features of the patients. There were seven male patients and one female patient. They ranged from 48 to 72 years in age (mean, 63.6). Hepatectomy was performed for cholangiocarcinoma (n = 3), adenocarcinoma of the gall bladder (n = 1), hepatocellular carcinoma (n = 1), metastatic colonic adenocarcinoma (n = 2), and one case of suspected cholangiocarcinoma (n = 1). Tumour was confirmed in the resected specimens except in case 4 (table 1). The tumour size ranged from 2 cm to 8 cm in greatest dimension (mean, 4.47). Portal vein thrombosis was noted on macroscopic examination in four cases (cases 4, 5, 7, and 8). The time interval between PVE and hepatectomy ranged from 15 days to 32 days. All patients were alive for a follow up period ranging from two to 21 months (mean, 8.6).

## Histological features

Histological examination showed cholangiocarcinoma (cases 1, 5, and 7), hepatocellular carcinoma (case 2), poorly differentiated adenocarcinoma of the gall bladder (case 3), and metastatic colonic adenocarcinoma (cases 6 and 8). No tumour was found in case 4. In addition, there were several light brown, irregular shaped saccular structures (parent bodies) enclosing small spherules (endobodies) within the portal veins in all eight cases (fig 1). These veins were denuded of endothelium, and replaced by granulation tissue and fibrous tissue with a lymphoplasmacytic infiltrate (fig 2).

**Abbreviations:** FLR, future liver remnant; PVE, portal vein embolisation

**Table 1** Clinicopathological features of the eight patients treated with portal vein embolisation

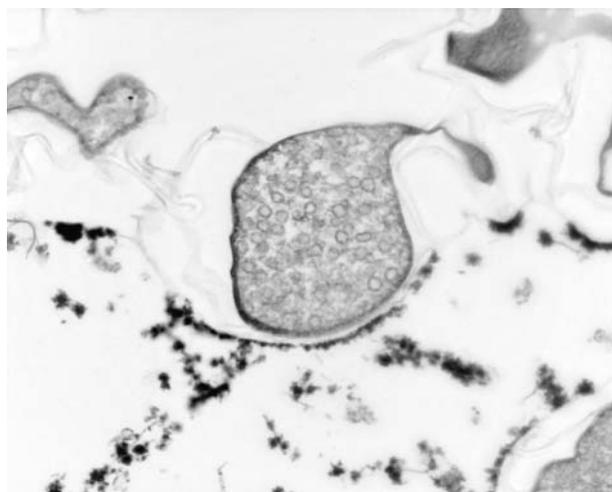
Case	Sex/age	Diagnosis	Tumour size (cm)	PVT (gross)	Interval between PVE and hepatectomy (days)	Follow up (months)
1	M/66	Cholangiocarcinoma	2.8×2×2	No	15	21
2	F/72	Hepatocellular carcinoma	8×8×5	No	21	16
3	M/69	Poorly differentiated adenocarcinoma of gall bladder	7.5×7×7	No	21	8
4	M/48	Suspected cholangiocarcinoma. No malignancy on resection		Yes	21	8
5	M/72	Cholangiocarcinoma	2.5×2.5×2	Yes	28	6
6	M/56	Metastatic colonic adenocarcinoma	5.5×4×3.5	No	22	4
7	M/56	Cholangiocarcinoma	2	Yes	32	4
8	M/70	Metastatic colonic adenocarcinoma	3×2.5×2.5	Yes	18	2

PVE, portal vein embolisation; PVT, portal vein thrombosis.

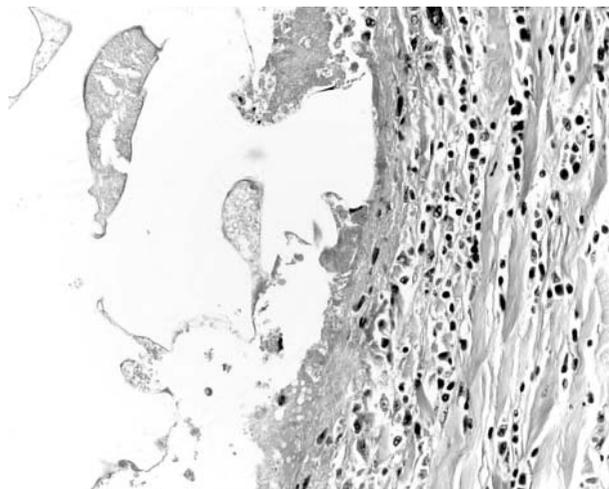
Foreign body-type giant cells (six cases; fig 3) and eosinophilic infiltrates (seven cases; fig 2) were noted in most cases. Both parent bodies and endobodies were stained red by Papanicolaou and Masson's trichrome, stained blue by solochrome cyanine, and were negative for Alcian blue, periodic acid Schiff, Grocott, and Ziehl-Neelsen stains. The endobodies showed immunoreactivity towards glycophorin A (fig 4). The overall features were those of myspherulosis.

## DISCUSSION

McClatchie *et al* in 1969 first described seven African patients with myspherulosis in skeletal muscle.<sup>3</sup> It is an uncommon condition characterised by the presence of numerous cystic spaces containing spheroid bodies on histological examination. This entity is called myspherulosis because such spheroid bodies have been mistaken as fungi. Since the original description, myspherulosis has been reported in different parts of the body, including the paranasal sinus,<sup>4-6</sup> eye,<sup>7</sup> brain,<sup>8</sup> dermis,<sup>9</sup> breast,<sup>10</sup> and renal adipose tissue.<sup>11</sup> Some forms are related to tumours, such as steatocystoma,<sup>12</sup> benign cystic teratoma,<sup>13</sup> and renal cell carcinoma.<sup>14</sup> The origin of myspherulosis has been studied extensively, and it has been suggested to result from the alteration of red blood cells<sup>4 15 16</sup> and macrophages.<sup>17</sup> The morphology, histochemical properties, and immunohistochemical profiles of the endobodies strongly suggest that they represent altered red blood cells. The parent bodies may be formed by the fusion of red blood cell membranes. Rosai<sup>4</sup> confirmed the origin of

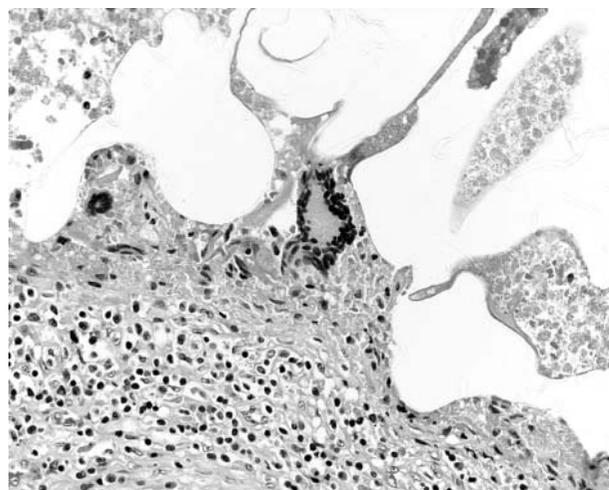


**Figure 1** High magnification photomicrograph showing aggregates of altered red cells (endobodies) surrounded by a thin membrane (parent bodies) (original magnification, ×40; haematoxylin and eosin stain).

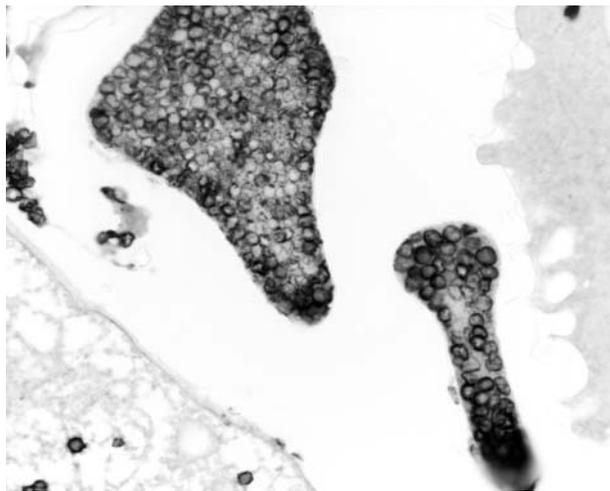


**Figure 2** Photomicrograph showing a denuded vein with lymphocytic and eosinophilic infiltrates. Spheroid bodies are encysted within small spaces in the vascular lumen (haematoxylin and eosin stain).

myspherulosis to be altered red cells by the experimental production of these spheroids by the action of tetracycline ointment on a pure preparation of human erythrocytes. Wheeler *et al* demonstrated the production of myspherules using either lanolin or petrolatum in vitro.<sup>16</sup> Kakizaki and



**Figure 3** Photomicrograph showing foreign body-type giant cells in the denuded vein (haematoxylin and eosin stain).



**Figure 4** Photomicrograph showing positive immunoreactivity towards glycoporphin A.

Shimada<sup>15</sup> showed that the parent body of myspherulosis was formed as a result of the physical emulsion phenomenon between lipid containing materials and blood. The parent body membrane was composed of the contents exuded from the altered red blood cells. The endobody comprises degenerate red blood cells with diameters of 5–7 µm, and was formed as a result of cell membrane pore formation during the process of red blood cell degeneration. Myspherulosis can be categorised as iatrogenic or endogenous, according to the origin of the lipid containing material. The iatrogenic type is usually caused by petroleum based material in therapeutic agents, such as oil based haemostatic packings, and the endogenous type is related to endogenous lipids, such as clear cell type renal cell carcinoma with a high lipid content.<sup>14</sup>

A mixture of butyl 2-cyanoacrylate (Histoacryl) and ethiodised oil (lipiodol) is used for portal vein embolisation in our centre. Butyl 2-cyanoacrylate is a cyanoacrylate adhesive. Cyanoacrylate compounds are used as surgical tissue adhesives or sclerosing agents. They are used as tubal occlusive agents for female sterilisation, for sclerotherapy in bleeding gastric varices, and for the embolisation of vascular lesions. Because cyanoacrylate compounds are radiopaque, they have to be used in conjunction with a radiopaque contrast material, such as ethiodised oil, for the visualisation and guidance of intravascular injections. Ethiodised oil is slowly metabolised to fatty acid and inorganic iodine. In one study, the mean biological half life of ethiodised oil I-131 ranged from 5.2 to 12.6 days.<sup>18</sup>

It appears that the metabolism of ethiodised oil into inorganic iodine and fatty acid plays a major role in the pathogenesis of myspherulosis in the liver. The administration of a mixture of butyl 2-cyanoacrylate and ethiodised oil into the portal vein causes thrombosis of the vessel (cyanoacrylate effect), resulting in the entrapment of red blood cells in an area of high concentration of ethiodised oil. Because the ethiodised oil is slowly metabolised into inorganic iodine and fatty acid, the prolonged contact between the fatty acid and the red blood cells results in the alteration and degeneration of the red blood cells to form parent bodies and endobodies in typical myspherulosis.

“It appears that the metabolism of ethiodised oil into inorganic iodine and fatty acid plays a major role in the pathogenesis of myspherulosis in the liver”

### Take home messages

- Hepatic myspherulosis is an under-recognised condition and should be considered if “spherules” are noted microscopically, in the context of portal vein thrombosis with ethiodised oil as contrast agent
- The endobodies of myspherulosis may be misdiagnosed as fungi or algae but the clinical history, intravascular location, lack of staining with periodic acid Schiff and Grocott stains, and positive glycoporphin A staining should point towards a diagnosis of myspherulosis

In these cases, the proposed mechanism mainly depends on two elements: the high concentration of the ethiodised oil and the time taken for its degradation. In our eight patients, the concentration of the chemical was kept constant and there were at least 15 days, more than one half life of the ethiodised oil, for such degradation to occur. It is reasonable to assume that the alteration and degeneration of the red blood cells might not occur if the time lapse between the embolisation procedure and hepatectomy were too short.

In our present study, there was no association between the tumour type and myspherulosis, as demonstrated by the consistent occurrence of myspherulosis in different kinds of tumours in the resected livers. Moreover, the presence of myspherulosis in the patient without tumour (case 4, table 1) confirms that the presence of tumour is not a prerequisite for the occurrence of myspherulosis.

The endobodies may be misdiagnosed as fungi or algae, such as coccidioidomycosis or Prototheca, by the unwary. However, the clinical history, intravascular location, lack of staining with periodic acid Schiff and Grocott stains, and positive glycoporphin A staining are generally sufficient to distinguish myspherulosis from fungi and algae.

In summary, hepatic myspherulosis is an under-recognised condition and should be considered if “spherules” are noted microscopically, in the context of portal vein thrombosis with ethiodised oil as contrast agent.

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