323

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PORTACAVAL SHUNT IN HYPERLIPOPROTEINÆMIA

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Summary A 12-year-old girl with homozygous type-II hyperlipoproteinæmia, which was refractory to medical treatment, had significant improvement in her serum lipid abnormalities during a trial of parenteral hyperalimentation. Subsequently, end-to-side portacaval shunt caused striking reduction of the serum-cholesterol and low-density (beta) lipoprotein elevations, regression or disappearance of xanthomatous skin and tendinous lesions during the 6½ months since operation, and relief of severe cardiac symptoms apparently as resorption occurred of xanthomatous deposits in the aortic valve and around the coronary arteries. Liver biopsy at 5½ months showed several changes, including depletion of rough endoplasmic reticulum; this finding was consistent with the possibility that the portal diversion caused the desired therapeutic effects by inhibiting synthesis of hepatic cholesterol or low-density lipoprotein.

INTRODUCTION

SYMPTOMATIC teenagers with homozygous type IIA hyperlipoproteinæmia have little chance of achieving a normal lifespan or even of reaching middle age.[1] Mautafis et al.[2] and Levy et al.[3] have reported reduction of serum-cholesterol in such patients after treatment with diet, cholestyramine, and nicotinic acid. However, the results were not predictable. An even less satisfactory experience has been recorded by others.[1-4]

We describe here the course of a 12-year-old girl with type IIA hyperlipoproteinæmia in whom a major myocardial infarction and significant aortic stenosis presumably due to xanthoma deposition developed despite therapy with diet, cholestyramine, dextrothyroxine, clofibrate, and nicotinic acid. An end-to-side portacaval shunt was performed with prompt and sustained regression of the hyperlipidæmia and hyperlipoproteinæmia, coupled with a remarkable subjective and objective clinical improvement over the ensuing 6½ months. The result will prompt us to recommend portal diversion for other patients with this disease who prove to be refractory to conventional therapy.

CASE-REPORT

A 12-year-old girl was first noted at age 6 months to have multiple yellowish lesions over her hands and feet. At age 3 years tuberous and tendinous xanthomas were noted and her cholesterol levels were found to vary between 850 and 950 mg. per 100 ml. Low-density (beta) lipoproteins were elevated and very-low density (pre-beta) lipoproteins were normal on electrophoresis. Triglyceride levels have always been normal. Three glucose-tolerance tests have been normal. Both parents and her only sibling were subsequently found to have elevated serum-cholesterol levels (father 350 mg. per 100 ml., mother 347 mg. per 100 ml., and her 14-year-old sister 395 mg. per 100 ml.). Her mother had had myocardial infarction at age 31 years.

Between the ages of 3 and 7 years the patient was treated with a low-fat diet, including a period of complete fat restriction in the hospital, with serum-cholesterol levels remaining above 600 mg. per 100 ml. In 1967, at age 7 years, she was given cholestyramine, 12 g. per day, and had a rise in the cholesterol level from 637 mg. per 100 ml. to 894 mg. per 100 ml. Prothrombin levels at that time fell from 100 to 70%. Dextrothyroxine (' Choloxin ') 2 mg. daily was also tried with no fall in the serum-cholesterol. Clofibrate (' Atromid-S ') treatment (0·5–1·0 g. twice daily) was tried between 1968 and 1972, at times in combination with nicotinic acid (200 mg. four times daily) or cholestyramine (' Questran ') (12–16 g. per day), with cholesterol levels remaining above 600 mg. per 100 ml. In 1972, a trial of cholestyramine therapy (12–16 g. per day) in combination with

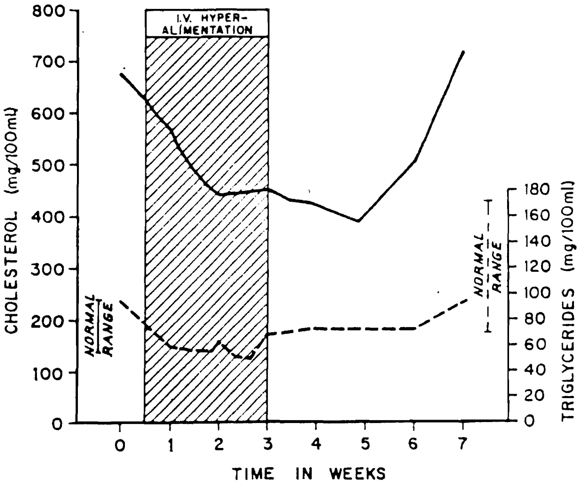

Fig. 1—Changes in cholesterol and triglycerides during intravenous hyperalimentation.

nicotinic acid, 800 mg. per day, also resulted in no fall in serum-cholesterol levels. For 3 months in 1972 she was given a synthetic no-cholesterol diet ('Vivonex'), with cholesterol levels remaining in the 600–700 mg. per 100 ml. range.

Finally, in November, 1972, she was treated with intravenous hyperalimentation (20% glucose, 3% aminoacids, minerals, and vitamins) for 3 weeks with minimal oral intake. Cholesterol gradually declined during the intravenous therapy and levels were repeatedly below 600 mg. per 100 ml. for the first time in her life (fig. 1). A low of 390 mg. per 100 ml. was attained 2 weeks after discontinuing the hyperalimentation, but levels soon rose again. Low-density-lipoprotein levels also fell during hyperalimentation, with pre-alimentation levels of 1019 and 1029 mg. per 100 ml., and a level of 322 mg. per 100 ml. 3 weeks after starting therapy. Triglyceride levels (fig. 1) are more difficult to evaluate since they were never elevated, but in comparison to the value of 97 mg. per 100 ml. just prior to treatment, or the mean of 9 fasting values of 95 ± 18 (S.D.) mg. per 100 ml. approximately a month later (see fig. 2), her levels during the intravenous hyperalimentation (60 ± 8 [S.D.] mg. per 100 ml.) were lower ($P < 0{\cdot}01$).

During the years of medical management, the xanthomatous lesions in the skin and elsewhere had continued to develop. At age 6 years, lipid masses were excised from the lower Achilles tendons, but these promptly returned. At age 7 years aortic stenosis was suspected

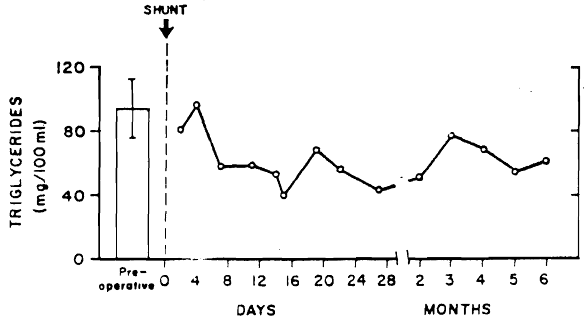

Fig. 2—Effect of portal diversion on triglyceride concentrations.

The normal range in our laboratory for this age is 70–120 mg. per 100 ml. The preoperative value represents the mean of 9 determinations ±one standard deviation.

because of an aortic systolic murmur and was confirmed by cardiac catheterisation. The gradient across the aortic valve was 24 mm. Hg. In November, 1972 (age 12 years, 2 months), cardiac catheterisation, which was repeated because of definite cardiac symptoms, showed that the gradient across the aortic valve had increased to 56 mm. Hg. On coronary arteriograms, the anterior descending and right coronary arteries showed generalised narrowing and the circumflex artery could not be displayed.

In December, 1972, the patient began to have progressively more severe angina pectoris as well as congestive heart-failure which could no longer be controlled despite therapy with nitroglycerin, digitalis, hydrodiuril, and spironolactone. In early February, 1973, she suffered acute anterior septal myocardial infarction. Because her condition was inexorably deteriorating, an end-to-side portacaval anastomosis was performed on March 1, 1973, in an effort to lower the serum-cholesterol levels. The anæsthesia, provided by Dr Henry Casson, was with intravenous diazepam ('Valium'), ketamine ('Ketalar'), and pancuronium ('Pavulon') combined with nitrous oxide/oxygen and enflurane ('Ethrane'). Although the patient was in severe heart-failure, the procedure was well tolerated.

Open biopsy of the liver was performed immediately before portal diversion, and a needle biopsy specimen was

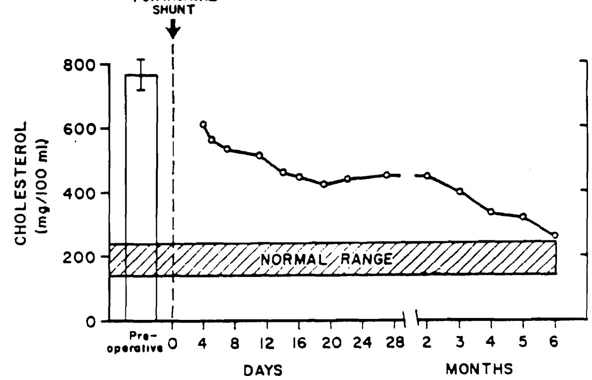

Fig. 3—Cholesterol concentrations before and 6 months after portal diversion.

The preoperative value represents the mean of 9 determinations ±one standard deviation.

taken 168 days later. One portion of each biopsy was fixed in 10% neutral formalin and was then processed for examination by light microscopy. A second piece of tissue was fixed in buffered glutaraldehyde, post-fixed in osmium tetroxide, and then embedded in 'Epon 812'. Sections for electron microscopy were stained with lead citrate and examined in a Philips 300 electron microscope. The sizes of the midzonal hepatocytes before and after portal diversion were determined on hæmatoxylin-and-eosin stained sections by a method previously described.[7] Midzonal hepatocytes identified in $0{\cdot}5\ \mu$ Epon sections were also used for measuring the rough endoplasmic reticulum length per area of cytoplasm by a morphometric method.[8,9]

RESULTS

On the low-cholesterol/high-polyunsaturated-fat diet that the patient has received most of her life, preoperative fasting serum-cholesterol levels, determined by the Liebermann-Burchardt colour reaction,[10] varied between 720 and 882 mg. per 100 ml., with a mean of 769 ± 47 (S.D.) mg. per 100 ml. (fig. 3).

During the same period in January and February, 1973, serum-triglyceride levels (fig. 2), determined by the method of Eggstein,[11] varied from 61 to 119 mg. per 100 ml. (mean 94 ± 18 [S.D.] mg. per 100 ml.). 4 days after operation her cholesterol value was 615 mg. per 100 ml., which was the last level above 600 mg. per 100 ml. (fig. 3). The value was 531 mg. per 100 ml. 1 week after operation and 462 mg. per 100 ml. after two weeks. The serum-cholesterol then remained between 402 and 454 mg. per 100 ml. until the 4th postoperative month, when it fell to 339 mg. per 100 ml. At the end of a half-year, it had declined to 239 mg. per 100 ml. (fig. 3). Triglyceride values ranged between 43 and 96 mg. per 100 ml. postoperatively, with a mean of 62 ± 16 mg. per 100 ml. (fig. 2). Postoperatively, both the cholesterol and triglyceride levels have been statistically lower than their respective preoperative levels ($P < 0{\cdot}01$).

Low-density-lipoprotein levels, determined by the method of Hatch et al.,[12] have decreased in parallel with the serum-cholesterol. Levels prior to surgery were consistently >1000 mg. per 100 ml., the value for the preoperative serum being 1163 mg. per 100 ml. The 6-month-postoperative level was 776 mg. per 100 ml.—still above the upper limits of normal of 579. Concurrently with the decline in blood lipoprotein and lipid levels has been the remission of cardiac symptoms. The patient has had no attacks of the previously refractory angina pectoris since the 2nd postoperative week and has returned to school and full activity. The intensity of the murmur of aortic stenosis has decreased. Her heart is still slightly enlarged but has decreased postoperatively. The skin xanthomas have almost entirely disappeared from her lower extremities, and the lesions over the remainder of the body are still regressing. There have been no adverse sequelæ, such as hepatic encephalopathy or hypoglycæmia, attributable to the portacaval shunt. She has gained 4·0 kg. in weight and 3 cm. in height in the 6 months after operation. Lipid-lowering drugs have not been restarted postoperatively and she currently receives no medications. She is on the same diet as preoperatively, but in due time consideration will be given to relaxing this.

The biopsy specimen obtained before portacaval diversion appeared normal by light microscopy. Ultrastructurally, hepatocytes sectioned through a central area showed many complexes of rough endoplasmic reticulum (fig. 4A). Each complex consisted of many parallel cisternæ of ribosome-studded membranes. Free polyribosomes were also present in the cytoplasm. Glycogen was abundant.

After portacaval diversion the size of the hepatocytes diminished significantly and the amount of fat in the cytoplasm of the liver cells increased. Ultrastructurally, the amount of rough endoplasmic reticulum was greatly reduced; only isolated profiles remained (figs. 4B and 4C). Morphometric analysis showed that the area of rough endoplasmic reticulum per volume of cytoplasm was reduced to about one-third the quantity found in the preoperative biopsy. The amount of smooth endoplasmic reticulum was not increased. Free ribosomes were relatively abundant. Glycogen particles were rare.

DISCUSSION

The diagnosis of homozygous type IIA hyperlipoproteinæmia was established in this patient by Fredrickson and Levy's major criteria.[1] First, she had the characteristic lipid profile in her plasma with an elevated low-density-lipoprotein concentration which was twice that of her heterozygotic parents and sister. Second, the type-II heterozygote pattern was demonstrated in the plasma of both her parents. In addition, all the minor diagnostic criteria were met, including the presence of subcutaneous and tendinous lesions before the age of 10 years, the appearance of vascular disease before the age of 20 years, plasma-cholesterol concentrations exceeding 500 mg. per 100 ml., normal triglyceride level, and no evidence of other diseases (hypothyroidism, pancreatitis, &c.) associated with hyperlipidæmia.

The refractoriness of the disorder to conservative management was indicated by the failure of a low-cholesterol diet or various medications singly or in combination to reduce the plasma-cholesterol and low-density-lipoprotein concentrations. Cholestyramine administered in 1967 actually caused an increase in serum-cholesterol concentrations, which was subsequently noted in two other children with type-II hyperlipoproteinæmia.[13] Despite strict management for more than 6 years, the patient's course was inexorably downhill, culminating in myocardial infarction, intractable heart-failure, and frequent attacks of angina pectoris.

The decision for portacaval shunt under these adverse conditions was an outgrowth of an earlier proposal to treat hepatic glycogen-storage disease by portal diversion.[14] In patients with type-I hepatic glycogenosis (hepatic glucose-6-phosphatase deficiency) it was observed that the characteristic hypertriglyceridæmia and frequent hypercholesterolæmia of this disorder were completely and permanently relieved by portacaval shunt.[15–17] In these type-I glycogen-storage patients, the hyperlipidæmia was also partially relieved in advance of portacaval shunt by a test period of parenteral hyperalimentation.[16,17] The same was true in the present case, providing some prior assurance of the wisdom of proceeding. The reduction in plasma-cholesterol concentration following 3 weeks of parenteral feeding was the greatest that had been achieved with this child during 6 years. After the intravenous alimentation was stopped, a return of the cholesterol to high levels was delayed for several weeks, suggesting that the explanation for the hyperalimentation effect was more complex than a more efficient peripheral utilisation of nutrients delivered intravenously.

The almost immediate fall in the plasma-cholesterol after end-to-side portacaval shunt was accompanied by a perceptible flattening of some of the skin lesions within 10 days. A comparable gradual but hæmodynamically significant melting away of xanthomatous lesions of the aortic valve and coronary arteries was thought to explain the relief of the cardiac symptoms. In the ensuing 6 months the skin lesions have regressed and the aortic systolic murmur has lessened. There has been no tendency for the hyperlipo-

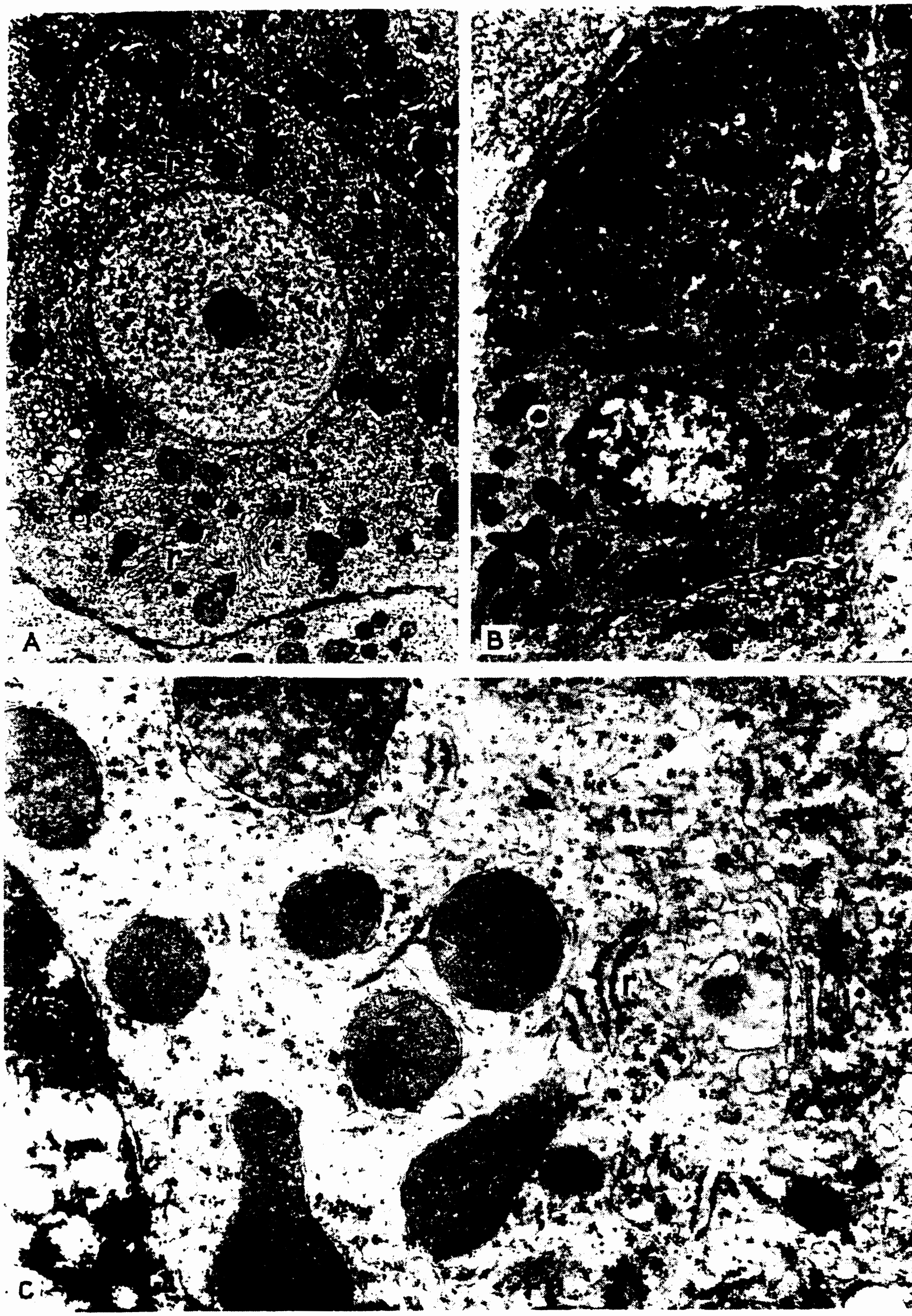

Fig. 4—Liver-biopsy appearances before (A) and after (B and C) portacaval shunt.

Rough endoplasmic reticulum (r) and glycogen are abundant in the preoperative biopsy. After portacaval anastomosis only isolated profiles of rough endoplasmic reticulum remain and glycogen is absent. Electron micrographs: A, ×3015; B, ×5575; C, ×25,100.

proteinæmia to recur. Rather, the plasma-cholesterol has slowly declined further from month to month.

The exact reason for the amelioration of hyperlipoproteinæmia in this patient is not known. The two most likely general causes of the disorder are, first, overproduction of cholesterol or low-density lipoproteins, or, second, deficient catabolism of these substances. In turn, the effect of portal diversion at either a hepatic or extrahepatic site on the production or destruction of either cholesterol or low-density lipoproteins theoretically could result from: (1) routing intestinal nutrients around the liver; (2) bypassing pancreatic hormones, particularly insulin and glucagon; or (3) a combination of (1) and (2).

Although the relative roles of bypassing intestinal nutrients versus the diversion of pancreatic hormones in the lowering of serum-cholesterol concentrations are not definable in our patient, animal experiments indicate in a general way that hormonal influences upon the liver are more profound than nutritional effects.[7] In these investigations, portions of dog livers were differentially exposed to venous blood returning from the intestines or alternatively to blood returning from the pancreatico/gastroduodeno/splenic area. By biochemical studies, the two liver sides were demonstrated to have drastically different compositions. Furthermore, the hepatic tissue perfused with the hormone-rich pancreatic blood soon underwent hypertrophy and hyperplasia in contrast to the hepatic fragment supplied with nutrient-rich intestinal blood. These observations prompted the conclusion that the hepatotrophic factors in portal venous blood, which we have previously stated to be important in maintaining hepatic structure and function,[18] are trace quantities of pancreatic hormones, particularly insulin and possibly glucagon as well.[7]

These experimental findings have made us postulate that the remarkable result in our patient was due most importantly to elimination of direct exposure of the liver to pancreatic hormones (especially insulin) and consequent reduction of the production phase of cholesterol and low-density lipoproteins. This hypothesis was supported by the pathological features of marked reduction of rough endoplasmic reticulum in our patient's liver biopsy $5\frac{1}{2}$ months after portacaval anastomosis. Studies by Jones et al.[19] on the synthesis of lipoproteins by the liver suggest that both rough and smooth endoplasmic reticulum are involved in this process. It will be important to elucidate these or other possible mechanisms, since with their understanding other forms of therapy may be devised.

In view of the dramatic result in this first case, the role of portal diversion in the treatment of hyperlipoproteinæmia will require careful definition. At present, portacaval-shunt surgery should be considered experimental and restricted to patients like this one who are refractory to dietary and medical therapy. As a last resort, at least in patients with homozygous type-II disease, portal diversion would seem to be simpler, and more permanently beneficial, than the ileal bypass procedures of Buchwald and Varco.[13,20,21] If portal diversion in humans with this kind of metabolic disorder proves to be tolerated as well as in patients with glycogen-storage disease, in whom portaprival complications such as hepatic encephalopathy have not been observed with follow-ups of up to a decade,[17] the indications for operative intervention for hyperlipidæmia may well become broader than those limited ones just suggested. Meanwhile, an exceptionally careful attitude about case selection will be necessary, since the long-term significance of the ultrastructural findings in the $5\frac{1}{2}$ month biopsy are not known.

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