High Serum Levels of Secretory IgA in Liver Disease

Possible Liver Origin of the Circulating Secretory Component

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Patients with liver disease frequently display unexplained elevations of serum secretory IgA (sIgA). The sIgA levels in various liver diseases were compared to various biochemical or clinical parameters. Patients with primary biliary cirrhosis, biliary tract obstruction, or acute hepatitis displayed highest sIgA levels. In chronic parenchymal liver disease sIgA levels correlated strongly with serum alkaline phosphatase (r = 0.79), leucine aminopeptidase (r = 0.83), and direct bilirubin levels (r = 0.63), but not with prothrombin time, aminopyrine breath test, or presence of portacaval shunting. In acute hepatitis sIgA correlated best with serum glutamic oxaloacetic transaminase (r = 0.69) but not with bilirubin; in four patients with fulminant hepatitis, sIgA fell rapidly together with all liver enzymes and prothrombin time; it rose quickly again in one patient when parenchymal regeneration occurred. These results suggest a hepatobiliary origin of the serum sIgA in liver disease. In acute hepatitis the persistence of hepatocytes seems necessary for maintaining high serum sIgA levels, suggesting a possible hepatocyte origin of the secretory component.

Normal adult serum contains about 2.5 mg/ml of IgA, mainly (90%) monomers, the remaining being dimers and larger polymers. This contrasts with secretions where the main immunoglobulin found is the 11 S secretory IgA (sIgA) (1, 2). Secretory component (SC) is an epithelial glycoprotein which acts as a membrane receptor for transepithelial transfer of polymeric immunoglobulins A and M into the secretions (3–6); free SC is also found in secretions (1). Minute amounts of sIgA are found in normal serum with mean levels reported from 5 to 40 μg/ml (7–10). Secretory IgM is only found in serum of IgA-deficient patients, and free SC is absent from normal and pathological sera (10–12, 17).

Elevations of sIgA in serum occur during lactation and in various pathological conditions (7–9, 13–15). However, only patients with liver disease (LD) display very high levels, up to 30 times the mean control values. Elevations observed in patients with other pathological conditions (celiac disease, inflammatory bowel disease, lung infection, neoplasms, rheumatoid arthritis, and myeloma) are irregular and small, up to five times the mean control value. Recently, we investigated most of these various conditions with a sensitive radio-

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TABLE 1. PATIENTS AND LIVER DISEASES

Diagnosis	*Number*	*Age (mean ± SD)*	*Sex ratio (m/f)*	*Remarks*
Acute viral hepatitis (AH)	21	48 ± 21	0.91	All with severe disease requiring hospitalization; 4 with submassive necrosis; 4 with massive necrosis
Alcoholic cirrhosis (AC)*	53	55 ± 10	1.3	4 with portacaval shunt
Chronic active liver disease (CALD)*	48	50 ± 16	0.65	
Chronic active hepatitis (CAH)*	8	41 ± 14	0.60	
Postnecrotic cirrhosis (PNC)*	40	52 ± 16	0.66	5 with portacaval shunt
Primary biliary cirrhosis (PBC)*	9	50 ± 9.6	0.12	2 with portacaval shunt
Biliary tract obstruction (BTO)	7	67 ± 10	0.75	2 pancreatic neoplasms; 5 stones of the common bile duct
Primary hepatic tumor (PT)	6	55 ± 12	1.0	5 hepatoma, all with cirrhosis; 1 vinyl chloride-induced angiosarcoma without cirrhosis
Miscellaneous liver diseases (MSC)	3	52 ± 7	2.0	2 primary sclerosing cholangitis and ulcerative colitis; 1 noncirrhotic portal hypertension and portacaval shunt

*All patients included under the group of chronic parenchymal liver disease (N = 110)

immunoassay (RIA) (16) and found sIgA levels above 30 μg/ml only in patients with LD, neoplasms with liver metastasis, or in lactating women (17). These high levels of circulating sIgA in patients with LD raise the question of the origin of the serum sIgA in patients with LD, as well as its clinical significance. We studied 147 patients with LD and compared their circulating sIgA levels with several biochemical or clinical parameters.

MATERIALS AND METHODS

Patients. The investigation involved 147 patients seen at the St-Luc Hospital between December 1978 and January 1980. They included 68 males and 79 females whose ages ranged from 18 to 81 years (mean 52 ± 13.5 years). In all instances the nature of LD was established according to clinical and biochemical criteria. Apart from the group with extrahepatic obstruction of the biliary tract, the diagnosis was confirmed by liver biopsy in all but 10 cases (3 alcoholic cirrhosis and 7 with the typical biochemical and serological picture of acute viral hepatitis). In 3 patients with acute hepatitis who died, postmortem liver histology was obtained. The presence or absence of cirrhosis was assessed by laparoscopy (nodularity of the liver) in all 110 cases of chronic parenchymal LD (CPLD). Furthermore, 22 of these patients also underwent hepatic vein catheterization for portohepatic pressure gradient measurement: wedged hepatic venous pressure minus free hepatic venous pressure (WHVP–FHVP) (18). When suspected, the presence and nature of biliary tract obstruction was confirmed and its site determined by endoscopic retrograde cholangiography, and in 4 patients by laparotomy. On the basis of complete clinical, biochemical, radiological, histological, or postmortem assessment, the patients were classified into the following groups: acute viral hepatitis (AH); alcoholic cirrhosis (AC); chronic active liver disease (CALD), including chronic active hepatitis (CAH) and postnecrotic cirrhosis (PNC); primary biliary cirrhosis (PBC); biliary tract obstruction (BTO); primary hepatic tumor (PT); miscellaneous (MSC). The clinical and pertinent additional features of these cases are listed in Table 1.

Clinical Biochemistry. All tests were done by routine laboratory tests of clinical biology on blood samples taken at the same time as those for sIgA measurement. Total serum IgA was measured by immunonephelometry (19) using a specific anti-human-α-chain antiserum, and expressed as a percentage of the control mean value (pool of over 1000 blood donors). Serum leucine aminopeptidase (LAP), alkaline phosphatase (AP), glutamic oxaloacetic transaminase (SGOT), total and direct-reacting bilirubin (SBR, DBR), were measured by a Technicon Autoanalyzer. Reagents used in AP and LAP assay were, respectively, *p*-nitrophenyl phosphate and L-leucine-*p*-nitranilide. The upper limit values of control ranges were 60 IU/liter (LAP), 75 IU/liter (AP), 35 IU/liter (SGOT), 1.1 mg/dl (SBR), and <0.2 mg/dl (DBR). The one-stage

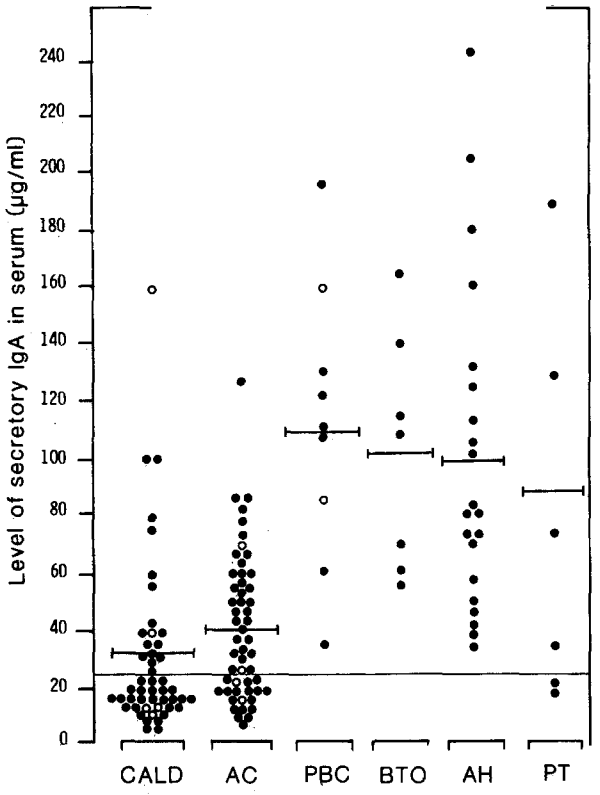

Fig 1. sIgA levels in patients with chronic active liver disease (CALD), alcoholic cirrhosis (AC), primary biliary cirrhosis (PBC), biliary tract obstruction (BTO), acute hepatitis (AH), and primary hepatic tumor (PT), without (•) or with (○) portacaval shunt. Individual values and means are shown. The horizontal line at 25 µg of sIgA per ml represents the upper limit (97.5 percentile) of the control population (N = 120).

prothrombin time of Quick (PTT) was used with lower value of control range at 60%.

The [^{14}C]aminopyrine breath test was performed by an adaptation (20) of the method of Hepner (21) in 65 patients with CPLD. Briefly, 1.0–1.5 µCi of [^{14}C]aminopyrine (15.9–30 mCi/mol, The Radiochemical Centre, Amersham, England) were administered intravenously to patients after an overnight fast. Breath samples were collected directly in counting vials containing 1 M hyamine hydroxide (methylbenzethonium hydroxide) in ethanol with phenolphthalein as indicator, before and 1 hr after injection, the patient being kept at rest throughout the test. The specific activity of the 1-hr sample, corrected for body weight, was expressed as the percentage of the injected dose. In 21 normal controls, the values ranged between 0.69% and 1.05% (mean ± SD: 0.86 ± 0.1).

The details of the RIA of sIgA in serum have been reported earlier (17). A goat antiserum was raised against purified free SC; it precipitated both free SC and sIgA, giving a reaction of identity. The IgG fraction of this goat anti-SC was used to coat plastic cups. Sera to be titrated were diluted at a constant 1:41 ratio in 20% horse serum in phosphate-buffered saline, containing appropriate amounts of highly purified ^{125}I-labeled milk 11 S sIgA. The mixture was then added to the cups in quadruplicate. After overnight incubation and washing, bound radioactivity was counted in a gamma counter. The same procedure was performed with cold sIgA (6–120 µg/ml in 100% horse serum) to construct a standard curve. When sera with high sIgA levels were diluted serially in 100% horse serum and then assayed, the values obtained closely followed the standard curve in all instances. The sIgA levels in sera from 120 clinically healthy blood donors ranged between 3.4 and 27.8 µg/ml (mean ± SD: 10.9 ± 4.6; 97.5 percentile: 25 µg/ml; intra- and interassay coefficients of variation for values ranging from 10 to 120 µg/ml: 2.6% and 3.7%, respectively.

Statistical Methods. All data are reported as mean ± 1 SD. The statistical significance of the observed changes and the coefficient of correlation (r) were determined by nonparametric methods, ie, the Wilcoxon sign rank test and the rank Spearman correlation coefficient, respectively.

RESULTS

Chronic Parenchymal Liver Disease (CPLD). The sIgA levels (Figure 1) found in patients with CALD (30 ± 29.6 µg/ml), AC (41 ± 25 µg/ml), and PBC (112 ± 42 µg/ml) were higher than controls (10.9 ± 4.6 µg/ml). All patients with PBC had elevated sIgA levels, with a significantly higher mean than patients with CALD ($P < 0.001$) and AC ($P < 0.001$). The mean value observed in AC was higher ($P < 0.005$) than that in CALD. Only six of the eleven cases with surgical portacaval shunt had elevated sIgA levels (Figure 1). The highest value (160 µg/ml) in the group with CALD was found in a patient with PNC and cholestasis related to azathioprine toxicity.

Among the biochemical parameters, AP (r = 0.79; $P < 0.001$) and LAP (r = 0.83; $P < 0.001$) (Figure 2) showed the best correlation with sIgA levels, followed by DBR (r = 0.63; $P < 0.001$), SGOT (r = 0.59; $P < 0.001$), and SBR (r = 0.48; $P < 0.001$) (Table 2). Of the eleven cases with portacaval shunt, only those with an elevation of one or both enzymes, AP and LAP, had increased serum sIgA levels.

Total IgA levels showed only a weak correlation with sIgA levels (r = 0.20; $P < 0.05$).

ABT and PTT did not significantly correlate with sIgA in the 65 patients studied (Table 2). When studying only 31 of these patients, selected for their absence of elevation of AP and LAP, again sIgA levels did not correlate significantly with PTT (r = 0.29) or ABT (r = 0.31). They also no longer correlated with SBR which showed, on this occa-

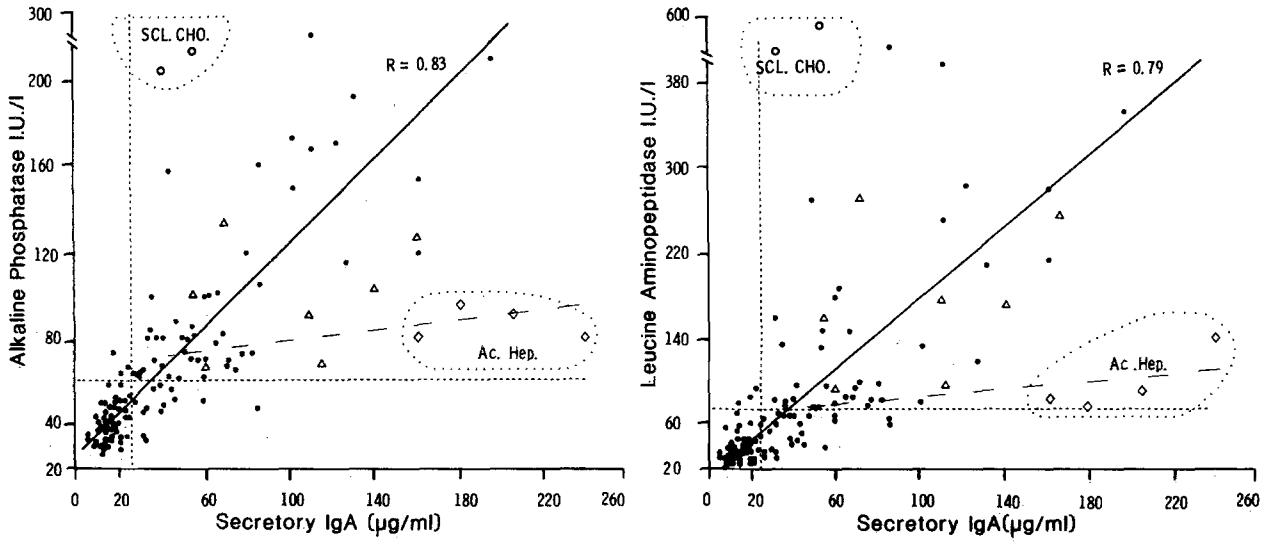

Fig 2. Correlations between values of sIgA and LAP (right) or AP (left) in 110 patients with chronic parenchymal LD (•). Data from patients with sclerosing cholangitis (○), AH (◇) and BTO (△) are not involved in the calculations of the correlation coefficients (*r*). Dotted lines represent the upper limits of control ranges. The dashed lines represent the linear regression in the whole group of AH.

sion, a good correlation with ABT ($r = 0.69$; $P < 0.01$). Figure 3 compares the levels of sIgA, SBR, and the results of ABT in these 31 patients without elevation of AP and LAP. In this group, the 7 patients with the lowest ABT values (< 0.1%), all with cirrhosis at a late state of evolution, presented low PTT values (not shown) ranging from 28 to 38% (31.5 ± 4%) and elevated SBR levels ranging from 1.5 to 9 mg/dl (3.5 ± 2.1 mg/dl). Five of these seven patients displayed obvious severe liver atrophy at laparoscopy. In spite of these indices of severity of liver dysfunction in these seven patients with normal AP and LAP levels, sIgA levels were only slightly elevated or were normal, ranging from 8 to 32 µg/ml (20.1 ± 6.6 µg/ml). The portohepatic pressure gradient (WHVP–FHVP) measured in 22 cases did not correlate with sIgA levels (Table 2).

Biliary Tract Obstruction (BTO). Patients with BTO also had sIgA levels (101 ± 40.6 µg/ml) higher than controls ($P < 0.001$), within the range of those found in PBC patients (Figure 1). The relationships between sIgA and AP or LAP were similar to those found in CPLD patients (Figure 2, triangles). In spite of the small size of the sample ($N = 7$), a significant correlation was found between sIgA and AP ($r = 0.82$; $P < 0.05$) or LAP ($r = 0.84$; $P < 0.05$).

Sclerosing Cholangitis. The two patients with sclerosing cholangitis had mild elevation of their sIgA levels (33 and 53 µg/ml). In spite of a normal level of SBR in both cases, extremely high levels of AP (455 and 603 IU/liter) and LAP (205 and 220 IU/liter) were found, much higher than those expected at the same sIgA levels in patients with CPLD and BTO (Figure 2, open circles).

TABLE 2. CORRELATION COEFFICIENT* BETWEEN SERUM SECRETORY IGA LEVELS AND OTHER PARAMETERS

	LAP	*AP*	*SGOT*	*DBR*	*SBR*	*IgA*	*PTT*	*ABT*	*(WHVP – FHVP)*
Chronic parenchymal liver diseases	0.83a $P < 0.001$	0.79a $P < 0.001$	0.59a $P < 0.001$	0.63a $P < 0.001$	0.48a $P < 0.001$	0.20a $P < 0.05$	0.19b NS	0.20b NS	0.34c NS
Acute hepatitis	0.55d $P < 0.01$	0.59d $P < 0.01$	0.69d $P < 0.001$	0.29d NS	0.21d NS				

*Rank Spearman coefficient of correlation; NS = $P > 0.05$. LAP: serum leucine aminopeptidase; AP: serum alkaline phosphatase; SGOT: serum glutamic oxaloacetic transaminases; DBR: serum direct bilirubin; SBR: serum total bilirubin; PTT: prothrombin time; ABT: aminopyrine breath test; (WHVP – FHVP): wedged hepatic venous pressure minus free hepatic venous pressure. a = 110 patients; b = 65 patients; c = 22 patients; d = 33 patients.

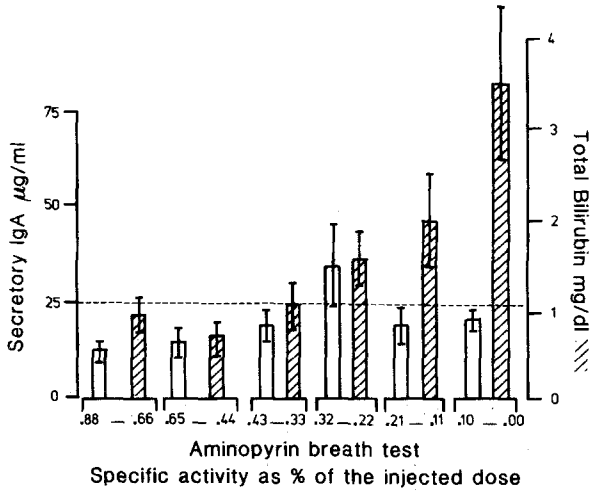

Fig 3. Comparative levels (mean ± SEM) of sIgA (open columns), SBR (shaded columns) and ABT values in 31 patients with chronic parenchymal LD without elevation of AP and LAP. Patients are divided into six arbitrary groups (N = 3–7) according to ranges of ABT values. Dotted line represents the upper limit of sIgA and SBR control ranges.

Primary Hepatic Tumor. Four of the five cases with hepatoma and CPLD had elevated levels of sIgA (Figure 1), AP, LAP, and SBR. All these parameters were normal in the fifth case, apart from AP (200 IU/liter). The patient with vinyl chloride-induced angiosarcoma displayed normal values for all these parameters.

Noncirrhotic Idiopathic Portal Hypertension. This single case of surgical portacaval shunt showed normal sIgA levels (8 µg/ml) without any biochemical sign of liver dysfunction.

Acute Parenchymal LD. Serum sIgA levels in patients with AH (99 ± 57 µg/ml) were, at the time of admission, higher than those of the controls ($P <$ 0.001), in the range found in PBC and BTO patients (Figure 1).

We studied the values of all cases on admission, together with those found 3 weeks later in 12 of them. The best correlation between sIgA and other biochemical parameters was found with SGOT (r = 0.69; $P < 0.001$) (Figure 4), followed by AP (r = 0.59; $P < 0.01$) and LAP (r = 0.55; $P < 0.01$). No significant correlation was found with DBR (r = 0.29) and SBR (r = 0.21) (Table 2). Patients with AH tended to display much higher sIgA values than those expected in patients with CPLD at the same levels of AP or LAP. This is well illustrated (Figure 2, lozenges) for the four AH patients with sIgA levels above 150 µg/ml, and by the significant ($P <$ 0.001 on t test) difference in the slopes of the regression lines (not all points relating to AH are shown in Figure 2 for clarity).

Four cases had a fulminant evolution with a rapid fall of PTT below 20%, progressive encephalopathy and coma, followed by death in three cases. The sIgA levels on admission were 52, 98, 65, and 42 µg/ml. They rapidly declined during the following days until 21, 27, 29, and 28 µg/ml, respectively, paralleling the fall of all the enzymes and PTT, although SBR remained high. In case 3, after falling to 29 µg/ml, sIgA rapidly rose again up to 96 µg/ml when signs of hepatocyte regeneration occurred (remission of encephalopathy and progressive normalization of PTT); also AP rose from 28 to 72 IU/liter and LAP from 25 to 78 IU/liter. Evolutions of sIgA, SGOT, AP, and SBR in three cases which were followed for more than five days are presented in Figure 5.

Serial studies in other nonfulminant cases showed persistent mild elevations of serum sIgA levels for prolonged periods of time, up to 3 weeks after normalization of all the other biochemical parameters.

DISCUSSION

The present study indicates that circulating sIgA levels rise in many cases of LD, this elevation being found in all our cases of AH as well as in those with PBC and BTO. The marked elevation we found in patients with extra- or intrahepatic cholestasis agrees well with previous reports (13, 22). However, contrary to these reports, we did not find a significant difference between sIgA levels in patients with BTO or PBC and those with AH. This lack of difference might be explained by the severity of disease in our cases of AH. In addition, these previous reports did not try to elucidate the origin of this elevation. In particular, they did not differentiate between, on the one hand, a decreased liver catabolism or clearance of peripheral (for instance gut) sIgA and, on the other hand, an escape into the circulation of SC or sIgA of hepatobiliary origin. For this purpose, two groups of our patients gave useful information.

First, in cases of CPLD, our data show an irregular elevation of serum sIgA which strongly correlates with LAP, AP, DB, and, to a lesser extent, with GOT and SBR. This confirms the relation between cholestasis and high sIgA levels. On the contrary we found no correlation between

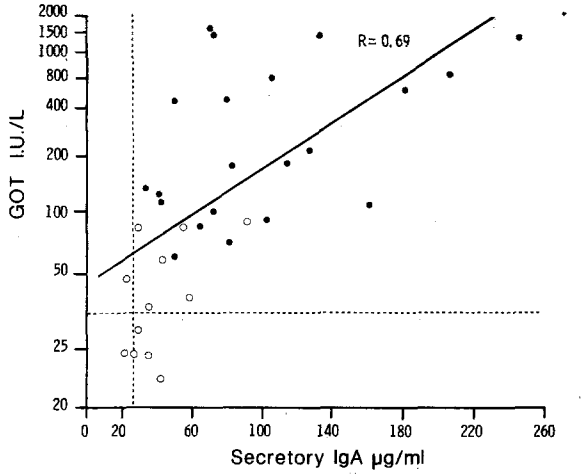

Fig 4. Linear regression between levels of sIgA and log levels of SGOT in patients with AH. Dotted lines represent the upper limits of control ranges. The correlation coefficient involved the 21 values on admission (●) and values obtained 3 weeks later (○) from 12 of these patients.

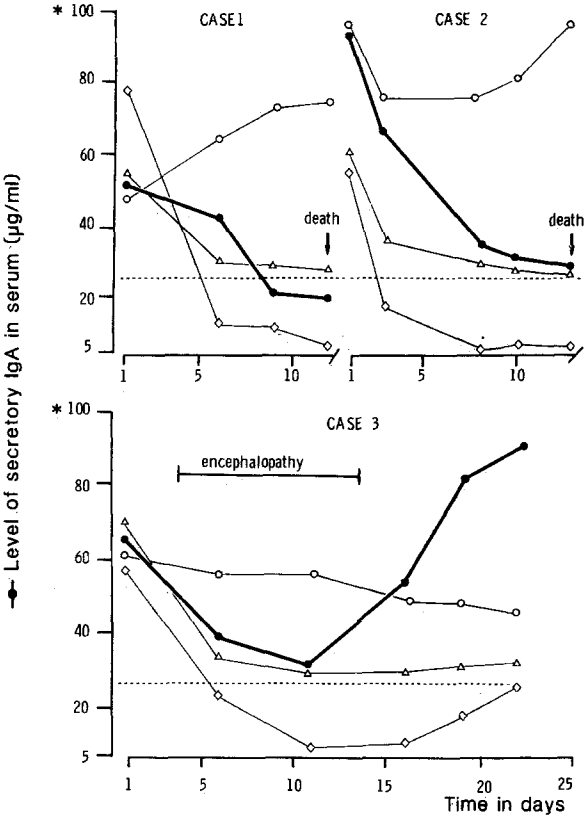

Fig 5. Evolution of levels of sIgA (●), AP (◇), SGOT (△) and SBR (○) in the three cases of fulminant AH followed for more than 5 days. The dotted lines represent the upper limits of all control ranges. The ordinates not only stand for sIgA levels, but also for AP (100* = 200 IU/liter), SGOT (100* = 1250 IU/liter), and SBR (100* = 40 mg/100ml).

sIgA elevation and the fall of PTT and ABT values, the elevation of SBR levels in patients without AP and LAP elevation, or presence of portacaval shunting. ABT and PTT represent useful indices of functioning liver parenchymal mass, quite independent of cholestasis in the case of ABT (23–25). The elevation of SBR in patients without AP and LAP elevation, but with advanced stages of cirrhosis, represents probably a decreased liver metabolism capacity, as suggested by its good correlation with ABT and PTT in these cases. Total IgA levels showed only a poor correlation with sIgA levels.

Secondly, in cases of AH, our data show constantly elevated serum sIgA levels, which strongly correlate with GOT and to a lesser extent with LAP and AP. They do not correlate with SBR and DBR. The lack of elevation of circulating sIgA when functioning parenchymal mass decreases is very well illustrated in the four cases of fulminant hepatitis which presented a fall of serum sIgA levels.

These results in CPLD and AH indicate that high levels of sIgA found in serum are not the consequence of a decreased liver clearance of the circulating sIgA. Indeed, in CPLD, increases in circulating sIgA levels correlate clinically and biochemically with the presence of cholestasis. If this elevation was the consequence of a decreased liver clearance of circulating peripheral sIgA, then elevated levels would be expected also in patients with markedly decreased functioning parenchymal mass, with the highest values in those with final evolution of massive parenchymal necrosis. Our results clearly indicate a lack of correlation between elevation of serum sIgA and decrease of functioning parenchymal mass. This rather suggests that, during liver disease, sIgA accumulates in serum either as a result of reflux from bile to serum of liver-assembled sIgA, or as a result of direct release, from the hepatobiliary tissue into plasma, of locally synthesized free SC. Free SC in serum binds preferentially to polymeric IgA (26, 27) in spite of its reported higher noncovalent affinity for IgM (28–30). For six patients with LD, the serum material reacting with our anti-SC antibodies was found, by density gradient ultracentrifugations, predominantly in an 11 S position, without any detectable free SC, and with 8–28% of 13–16 S material; a small amount (5%) of material heavier than 16 S was demonstrated in one case (17).

In addition, our data suggest that the hepatocyte itself might well represent a significant source of SC. Indeed, in acute as well as in CPLD, a strong correlation appears between sIgA levels and liver enzymes, GOT, LAP, and AP. Among the hepatobiliary tissues all these enzymes are found mainly in and on the hepatocytes. Immunohistochemical studies have shown the main localization of AP and LAP in the sinusoidal and canalicular membrane of the hepatocyte and to a lesser extent in the microsomal fraction of these cells. The mechanism by which they reach the blood during cholestasis remains unknown (31–34). Furthermore, the typical evolution of sIgA levels during massive parenchymal necrosis highlights the possible dominant role of the hepatocyte in generation of high circulating sIgA levels. It suggests, as shown for cultivated rat hepatocytes (35, 36), that the human hepatocyte itself might synthesize the SC. The characteristic histological aspect of the liver in fulminant massive necrosis, showing the disappearance of hepatocytes with persistant bile ducts, represents a strong, albeit indirect, argument for an hepatocyte origin of SC. This would explain the fall of circulating sIgA levels and its subsequent elevation in the case which showed clinical and biochemical evidence of hepatocyte regeneration. However, although rat immunohistochemical studies have shown the SC in and on both hepatocytes and biliary epithelium (37, 38), similar studies in humans showed the SC and IgA only in the biliary epithelial cells (37, 39).

In conclusion, sIgA accumulates in serum of patients with LD and probably originates from the hepatobiliary tissues. Our results suggest that the circulating SC might originate in part from the hepatocytes. The increase of serum sIgA does not allow us to differentiate between intra- or extrahepatic cholestasis.

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