

A Novel Type of Selective Immunoglobulin M Deficiency in a Patient with Autoimmune Liver Cirrhosis with Recurrent Hepatocellular Carcinoma: A Case Report and Review of the Literature

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Established Facts

- Most previous reports on adult selective immunoglobulin (Ig) M deficiency (at low but detectable levels) showed normal serum IgG and IgA levels and were often complicated with severe bacterial infections.
- Most of the previous reports are associated systemic autoimmune diseases or malignancies.
- Dysfunctions of helper T cells or intrinsic B cell abnormality could be the possible mechanism for selective IgM deficiency.

Novel Insights

- A female, aged over 60, showing undetectable serum levels of IgM with high serum levels of both IgG and IgA had never experienced severe bacterial infections.
- Liver cirrhosis from autoimmune hepatitis could be associated with selective IgM deficiency.
- Enhanced class switching of immunoglobulins due to overexpression of activation-induced cytidine deaminase could be a mechanism for selective IgM deficiency with high serum levels of IgG and IgA.
- All previous reports (based on PubMed) on adult-selective IgM deficiency cases were summarized for the first time.

Key Words

Selective immunoglobulin M deficiency · Liver cancer · Autoimmune hepatitis · Activation-induced cytidine deaminase

Abstract

A 64-year-old female with advanced liver cirrhosis who had never experienced severe infections presented in 2004 with general malaise. At the time, her serum showed low levels of

immunoglobulin (Ig) M (11 mg/dl) with high levels of both IgG (2,942 mg/dl) and IgA (808 mg/dl). Because serum levels of IgG and IgA in previous cases of selective IgM deficiency were normal, this case could have a novel immunological mechanism. By 2006, serum IgM was undetectable (<5 mg/dl). Liver biopsy showed liver cirrhosis from autoimmune hepatitis. She had no other autoimmune diseases or hematological malignancies. She developed hepatocellular carcinoma (HCC) several times and died of liver failure. Immunological analyses performed before the first diagnosis of HCC

showed polyclonal γ -globulin elevation, normal chromosome and normal gene rearrangement of immunoglobulin heavy chain C μ . Peripheral blood showed low count B cells with few surface IgM-positive B lymphocytes, but the percentages of T cell subsets were normal. Expression of activation-induced cytidine deaminase (AID), which plays a critical role in immunoglobulin class switching, was found to be overexpressed in the HCC tissue and B cells in bone marrow. This phenomenon could account for the clinical and immunological features of this case. In conclusion, we propose a novel type of selective IgM deficiency in association with the overexpression of AID.

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Introduction

Selective immunoglobulin (Ig) M deficiency is a rare disorder associated with severe bacterial infections, autoimmune diseases and malignancies of heterogeneous pathogenesis [1–2]. Serum levels of IgG and IgA are normal in such patients and the possible pathogenesis of isolated failure of IgM production such as dysfunctions of helper T cells or intrinsic B cell abnormality has been proposed [3–5]. We present a novel type of selective IgM deficiency possibly associated with the overexpression of activation-induced cytidine deaminase (AID).

Case Report

A 64-year-old female with advanced liver cirrhosis (Child-Pugh grade B) who had never experienced severe infections presented in 2004 with general malaise. At the time, her serum showed low levels of IgM (11 mg/dl) with high levels of both IgG (2,942 mg/dl) and IgA (808 mg/dl). By 2006, serum IgM was undetectable (<5 mg/dl), indicating an acquired IgM deficiency, and the levels of IgG and IgA remained high during the course (table 1). She was positive for anti-nuclear antibody at a titer of 1:160 (homogenous and speckled pattern), negative for HBsAg, anti-HBc, HBV DNA and anti-HCV. Anti-smooth-muscle antibody, anti-mitochondrial antibody and antibody to liver/kidney microsome type 1 were also negative. Her ferritin, ceruloplasmin, copper and α 1-antitrypsin levels in the serum were within normal ranges. These data exclude the presence of viral hepatitis, primary biliary cirrhosis, type 2 autoimmune hepatitis (AIH), hemochromatosis, Wilson's disease and α 1-antitrypsin deficiency as underlying diseases. She did not drink alcohol and her BMI was normal, i.e. this excludes alcoholic liver injury or nonalcoholic steatohepatitis. She had taken ursodeoxycholic acid, but had refused to take corticosteroids because of side effects. In 2008, she experienced a spontaneous rupture of the esophagus (Boerhaave syndrome), but recovered with antimicrobial agents without complications of severe bacterial infection. In 2009, her serum α -feto-

protein (AFP) level was suddenly elevated to 132.1 ng/ml (table 1) and an abdominal CT scan revealed a 1.5-cm-diameter tumor in S8 of her liver. A biopsy showed moderately differentiated hepatocellular carcinoma (HCC) (fig. 1a) accompanying advanced fibrosis and marked necroinflammation (fig. 1b), compatible with liver cirrhosis from AIH. Furthermore, assessed by the original and simplified scoring system of the international autoimmune hepatitis group [6, 7], she was scored as definite for AIH, indicating that her liver cirrhosis was indeed from this (type 1). She had no symptoms and signs of other autoimmune diseases. Her HCC was treated by radiofrequency ablation with a rapid decrease in the level of AFP to below 20 ng/ml. Although stable for 6 months after the first ablation, HCC frequently recurred thereafter in separated areas until she was lost to liver failure in November 2010 (table 1).

Immunological analyses were performed to clarify the mechanism of selective IgM deficiency in August 2009. IgM deficiency with high concentrations of γ -globulin in a polyclonal pattern was confirmed by electrophoresis analysis (fig. 1c, d) and the presence of serum inhibitory factor for the detection of IgM was ruled out by a competition assay (data not shown). Her chromosome (data not shown) and gene rearrangement of immunoglobulin heavy chain (IgH) C μ were normal (fig. 1e) and no hematological malignancies were detected in a bone marrow analysis. Flow cytometric analysis of peripheral blood showed low-count B cells (2%) with few surface IgM-positive B lymphocytes and normal rates of CD4 $^{+}$ and CD8 $^{+}$ T lymphocytes (42.7 and 41.7%, respectively) or CD4 $^{+}$ CD25 $^{+}$ lymphocytes (12.8%). These data indicate her level of serum IgM fell due to defective IgM-producing B lymphocytes, rather than due to altered T cell subsets.

Discussion

There is no definite evidence whether the selective IgM deficiency in this case was hereditary or acquired, because there are no data on her immunoglobulins before 2004. However, a gradual decrease of serum IgM was observed after 60 years of age, and a normal recombination of IgH C μ gene was proved by Southern blot analysis, suggesting that she had an acquired type of selective IgM deficiency. All previous reports on adult selective IgM deficiency based on PubMed searches have been summarized in table 2 [2–4, 8–21]. Our case presents some unique clinical characteristics in comparison. Most of the previous reports revealed normal levels of IgG and IgA accompanying a low level of IgM, whereas our case showed high levels of IgG and IgA with undetectable IgM. Moreover, the patient had never experienced severe bacterial infections, in spite of low or undetectable serum IgM levels over several years. Although it could be possible that acquired IgM deficiency occurred secondary to systemic autoimmune disease or malignant disease (table 2), she showed no symptoms and signs of systemic autoimmune disease, and there has been no re-

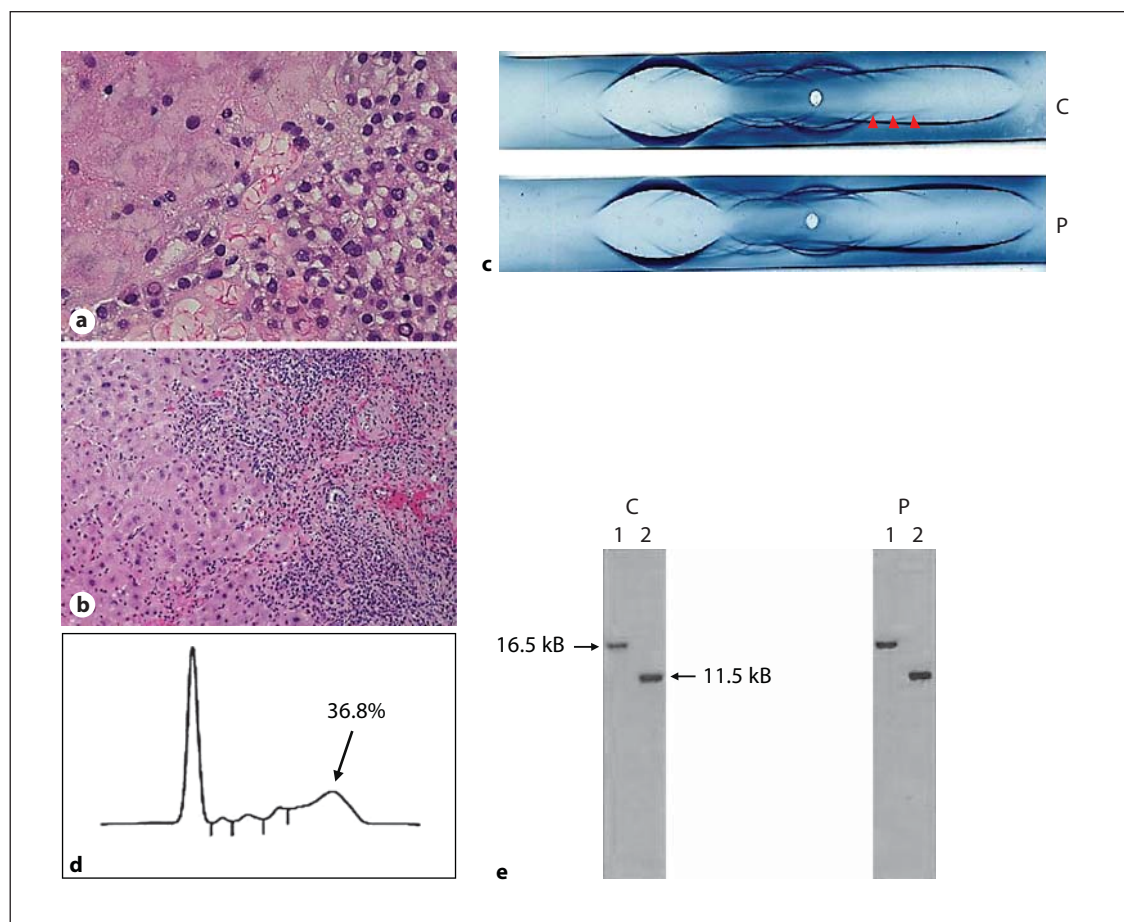


Fig. 1. **a** Histology of HCC and adjacent nontumor tissue, liver biopsy specimen (original magnification $\times 400$). **b** Histology of nontumor tissue showing marked necroinflammation with interface hepatitis (original magnification $\times 100$). **c** Electrophoresis analysis of the serum of the patient (P) and a healthy control (C) showing defect of IgM in the patient. **d** Electrophoresis of patient serum showing elevated proportion of γ -globulin in a polyclonal pattern. **e** Gene rearrangement of IgH C μ of peripheral blood lymphocytes analyzed by Southern blotting after digestion with restriction enzymes. 1 = *Bam*HI-digested and 2 = *Hind*III-digested.

Table 1. Temporal changes in serum levels of immunoglobulins, anti-nuclear antibody, AFP and development of HCC

	Normal limits	May 2004	December 2004	September 2006	August 2009	November 2009	April 2010	June 2010	September 2010
IgA, mg/dl	110–410	808	801	625	669			825	
IgM, mg/dl	46–260	11	8	<5	<5			<5	
IgG, mg/dl	870–1,700	2,942	2,689	2,635	2,432			2,987	
ANA, FA			$\times 160$	$\times 160$	$\times 160$			$\times 160$	
Homogenous			$\times 160$	$\times 160$	$\times 160$			$\times 160$	
Speckled			$\times 160$	$\times 160$	$\times 160$			$\times 160$	
Nucleolar			$< \times 40$	$< \times 40$	$< \times 40$			$\times 80$	
AFP, ng/ml	0–10	10.3	9.5	13.9	132.1	7.5	39.1	106.4	2867.3
HCCs, n (location)					1 (S8)		1 (S7)	1 (S4)	4 (S4, S7)
Treatment					RFA		RFA	PEI	PEI

ANA = Anti-nuclear antibody; FA = fluorescence analysis; PEI = percutaneous ethanol injection; RFA = radiofrequency ablation; S = segment of the liver.

Table 2. Reported cases of adult selective IgM deficiency with associated disorders

Associated conditions	Disease	n	Age	Sex	IgM	IgG	IgA	Ref.
Neoplasm or hematologic disorders	SCC (skin)	1	20	M	33.6	w.n.l.	w.n.l.	[8]
	Clear cell sarcoma (Achilles tendon)	1	58	F	<1	2,540	1,500	[9]
	Leiomyoma	1	66	M	8	850	253	[10]
	Bronchial polyp	1	37	M	3.0	1,156	291	[11]
	Nasal polyposis	1	23	M	28	w.n.l.	w.n.l.	[12]
	Bloom's syndrome ¹	3	21	F	48	1,063	212	[13]
			21	M	28	1,166	233	[14]
			19	F	48	1,036	212	[14]
	Lymphoma	2	60	F	8	1,707	326	[3]
			75	F	14	1,080	69	[2]
	Prolymphocytic leukemia	1	47	M	40	1,520	437	[15]
Autoimmune disorders	SLE	16	51	F	10	2,340	312	[3]
			51	F	<46	1,010	535	[16]
			43	F	5	1,426	389	[17]
			37	F	15	1,506	508	[17]
			33	F	17	1,532	340	[17]
			47	F	23	1,567	298	[17]
			41	F	25	1,900	522	[17]
			42	F	28	1,316	280	[17]
			36	M	30	1,267	443	[17]
			59	F	32	2,546	352	[17]
			30	F	37	1,109	240	[17]
			63	F	43	1,319	300	[17]
			36	F	44	1,226	433	[17]
			55	F	44	1,441	221	[17]
			29	F	25	1,597	203	[4]
			30	M	6	936	221	[4]
	Autoimmune glomerulonephritis	1	57	M	34.1	1,500	843	[18]
	Hashimoto's thyroiditis	2	70	M	<3	1,972	233	[19]
			50	F	34	921	105	[2]
	Hypothyroidism	1	39	F	16	729	118	[2]
	Psoriasis pustulosa	1	34	M	1	1,314	168	[5]
	Rheumatoid arthritis	2	53	F	17	2,159	612	[4]
			46	F	39	985	160	[2]
	Rheumatic heart disease	1	48	M	21	790	228	[20]
	Celiac disease	3	23	M	48	2,100	420	[21]
			26	M	27	1,700	420	[21]
			75	M	48	1,200	320	[21]
Our case	AIH, HCC	1	64	F	11	2,942	808	

SCC = Squamous cell carcinoma; SLE = systemic lupus erythematosus; w.n.l. = within normal limits.

¹ Bloom's syndrome is a rare autosomal recessive chromosomal disorder with a high risk of cancer and selective IgM deficiency [14].

port of selective IgM deficiency accompanied by autoimmune hepatitis. Moreover, IgM deficiency had been observed 5 years before the development of HCC, indicating that HCC was not the cause of IgM deficiency in this case.

A possible mechanism that might account for these features is enhanced immunoglobulin class switching

from IgM-positive to IgG-positive or IgA-positive B lymphocytes accelerated by an unknown factor leading to the maintenance of the defense mechanism against microbes. Recently, an enzyme that plays a critical role in immunoglobulin class switching was identified, namely AID [22]. Aberrant expression of AID in non-lymphoid cells was associated with a high rate of carci-

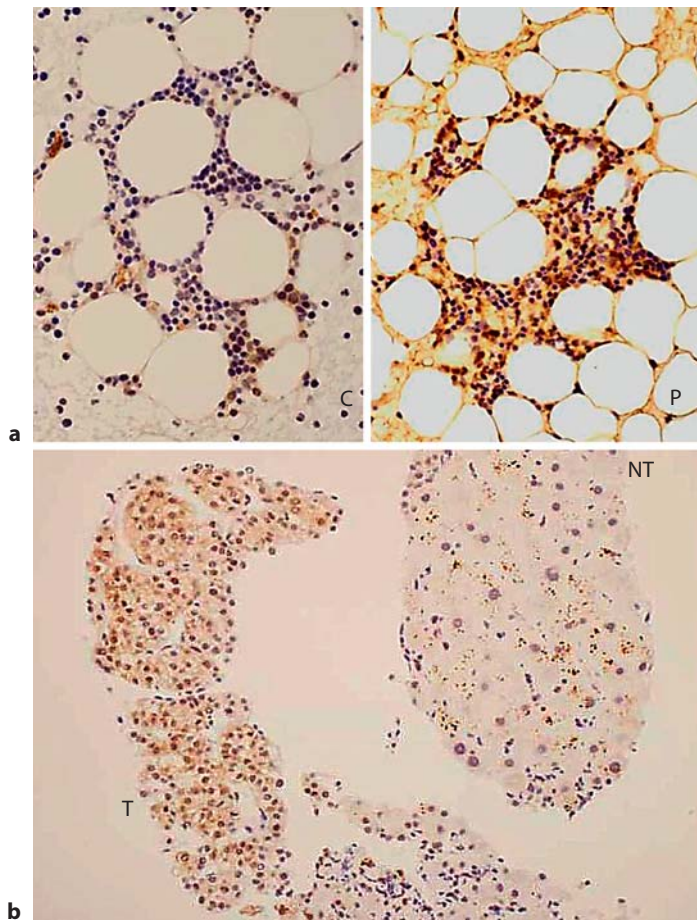


Fig. 2. **a** Immunohistochemical study of AID expression in bone marrow of the patient (P) and a healthy control (C) (original magnification $\times 200$). **b** Immunohistochemical study of AID expression in a liver with HCC (T) and in nontumor tissue (NT) (original magnification $\times 200$).

nogenesis following enhanced mutagenesis [23]. Immunohistochemical study revealed that AID was overexpressed in the bone marrow, mostly CD79a+ B cells (data not shown), compared to that of controls (fig. 2a). AID was also expressed in HCC tissues but not in nontumor liver tissue (fig. 2b). This phenomenon could account for the unique clinical features in this case, including the recurrence of HCC. AID has been reported to be induced by proinflammatory cytokines such as tumor necrosis factor- α or transforming growth factor- β as the consequence of chronic inflammation, leading to carcinogenesis including HCC [23, 24]. In this case, it is unlikely that chronic inflammation of autoimmune hepatitis induced AID production, because nontumor liver tissue did not show an overexpression of AID. Therefore, the mechanism responsible for AID overexpression in bone marrow and HCC tissue in this case is currently unclear.

Conclusion

We propose a novel type of selective IgM deficiency in association with an overexpression of AID as a possible cause of isolated failure of IgM production with overproduction of other immunoglobulins.

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