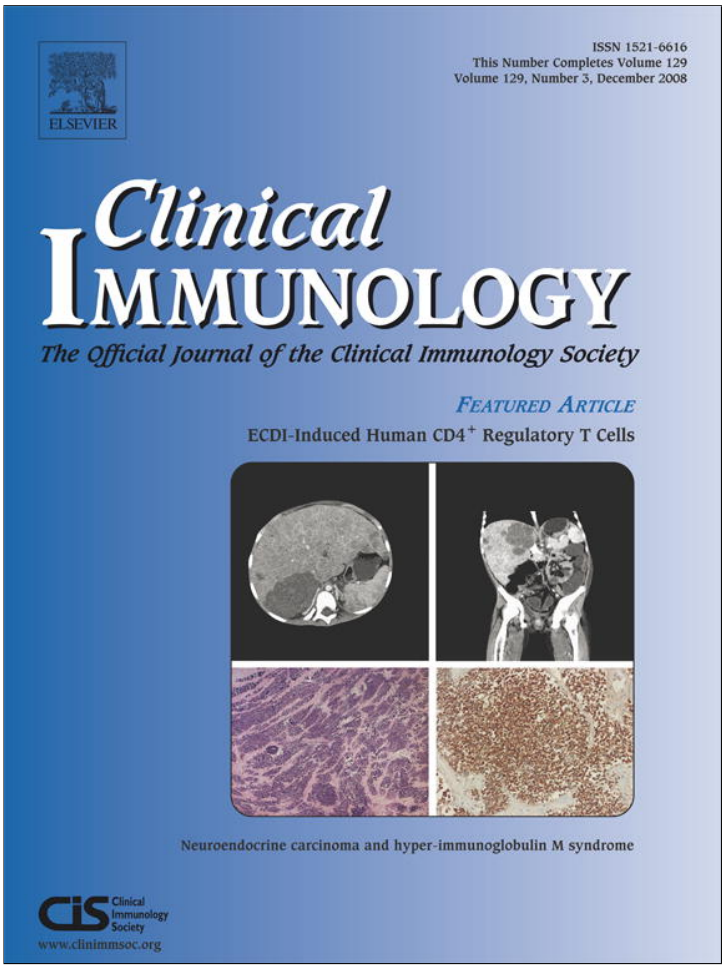

Clinical Immunology (2008) **129**, 455–461

available at www.sciencedirect.com

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Neuroendocrine carcinoma associated with X-linked hyper-immunoglobulin M syndrome: Report of four cases and review of the literature

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Received 2 July 2008; accepted with revision 5 August 2008
Available online 20 September 2008

KEYWORDS
Hyper-IgM syndrome;
CD40 ligand deficiency;
Neuroendocrine carcinoma

Abstract X-linked hyper-immunoglobulin M syndrome (XHIGM) is a primary immunodeficiency disorder characterized by severe defects of both cellular and humoral immunity due to impaired expression of CD40 ligand on activated T lymphocytes. Patients with XHIGM usually present with a wide variety of infections caused by common and opportunistic pathogens including *Pneumocystis jirovecii*. In addition, subjects with XHIGM have an increased risk for hepatocellular and bile duct carcinomas, which are rarely observed in other primary immunodeficiencies. We present here clinical, immunological, and molecular findings of four patients with CD40 ligand deficiency associated with neuroendocrine carcinoma (NEC). NEC developed as a rapidly disseminated solid cancer leading to death in three patients. Data presented here and published previously suggest that CD40 ligand deficiency may predispose patients for the development of NEC. Histochemical findings suggested that CD56, in addition to cytokeratin and chromogranin A, may be a useful marker for early detection of NEC. We conclude that patients with XHIGM should be carefully followed to diagnose and treat NEC, a formidable neuroendocrine cancer.

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1521-6616/$ – see front matter
doi:10.1016/j.clim.2008.08.005

Introduction

X-linked hyper-immunoglobulin M syndrome (XHIGM) is a primary immunodeficiency disorder (PID) characterized by extremely low levels of serum IgG and IgA, and normal or increased level of serum IgM [1,2]. XHIGM is caused by mutations in the gene encoding for CD40 ligand (CD40L), a transmembrane protein expressed by activated T cells [3]. Patients with CD40L deficiency usually present within the first 2 years of life with recurrent sinopulmonary and gastrointestinal tract infections, growth failure, persistent or cyclic neutropenia, stomatitis, *Pneumocystis jirovecii* pneumonia, and sclerosing cholangitis [4]. Hepatocellular carcinoma and bile duct carcinoma have also been reported as complications of XHIGM [4–6].

Neuroendocrine carcinoma (NEC) is a rare tumor with varying clinical course and biological behavior [7]. It is mostly localized to the appendix or the colon but may also occur at extraappendicular sites. We have recently diagnosed NEC in one of the Hungarian patients with XHIGM (Case 1 in this report). To define primary immunodeficiency diseases that may also associate with NEC we performed an automated PubMed search and found 7 published cases [5,8–11]. Colonic NEC associated with PID was first described in a 16-year-old patient with common variable immunodeficiency [8]. Sasi et al. published recently another patient who had X-linked agammaglobulinemia and developed colonic NEC [9]. Five further case reports suggested that NEC may also develop in patients with XHIGM [5,10,11]. Utilizing the European Society for Immunodeficiencies online database for clinical and laboratory data from 64 documenting centers in 29 countries we found four (including Case 1) out of 6,965 registered patients who developed undifferentiated NEC [12]. Intriguingly, all of these patients had XHIGM as the underlying PID. We present here clinical, immunological, and molecular data of these four patients. Based on this study and previous reports we propose that NEC may associate with XHIGM more commonly than with any other primary immunodeficiencies. Our report suggests that XHIGM may predispose patients, in addition to hepatocellular and bile duct carcinoma, to neuroendocrine tumors.

Methods

Immunochemistry and flow cytometry

Serum immunoglobulin isotypes were quantified by using standard laboratory assay. Flow cytometry analysis was applied to detect surface marker expression on T cells (CD3, CD4, CD8, CD40L), B cells (CD19, CD40), and NK cells (CD56). For the analysis of CD40L expression, peripheral blood mononuclear cells were activated with phorbol myristate acetate and ionomycin [13].

Histology

Tissue samples were fixed in formalin and embedded in paraplast. Sections were stained with hematoxylin and eosin, and investigated by immunohistochemical methods. Immunostaining was performed by using monoclonal antibodies to cytokeratin (DAKO), chromogranin A (DAKO), and CD56 (Novocastra), and a streptavidin–biotin peroxidase system.

DNA sequencing

Isolation and sequencing of genomic DNA was performed by standard molecular genetic assays. *CD40L* exons and the flanking intron regions were amplified by primer sequences and PCR amplification. Mutational analysis was performed by using the BigDye Terminator Cycle sequencing kit (Applied Biosystems, Foster City, CA) and an ABI PRISM 3130 Genetic Analyzer (Applied Biosystems, Foster City, CA). The cDNA nucleotide sequences were numbered from the upstream initiator ATG codon.

Imaging techniques

Computed tomography (CT) was carried out by using a LightSpeed 16 multislice CT scanner (General Electric). During diagnostic CT examination intravenous contrast media was used to detect the contrast enhancement in the tissue lesion. For magnetic resonance imaging (MRI) a Signa Excite 1.5T scanner was applied (General Electric). Axial, coronal and sagittal images were acquired from the entire abdomen. T1 and T2 weighted images were generated using gradient echo, single shot fast spin echo, fast spoiled gradient echo, and Fiesta sequences with or without fat saturation.

Results

Immunological and genetic characteristics of patients

Four patients with XHIGM syndrome associated with NEC are reported in this study (Table 1). All studies were performed

Table 1 Immunological and genetics characteristics of patients

Characteristics	Case 1	Case 2	Case 3	Case 4
Immunoglobulin isotypes (g/L)				
IgG (4.9–16.1)	0.85	0.79	0.61	0.19
IgA (0.5–2.8)	0.23	0.06	0.06	0.01
IgM (0.5–2.0)	1.61	0.4	NA	0.81
Expression of CD40L on activated T cells	0.05%	Negligible	Negligible	Negligible
Sequence variants of the *CD40L* gene	c.694C>T	c.482T>G	c.204insC	NA
Protein change of CD40L	p.Q232X	p.L161R	p.T68TfsC84X	NA

For the analysis of CD40L expression, peripheral blood mononuclear cells were activated with phorbol myristate acetate and ionomycin [13]. NA, not available. Normal ranges of immunoglobulin isotypes in children aged 3–15 years are indicated in brackets.

with the informed consent of the patients or of their parents. The diagnosis of XHIGM was defined by markedly diminished serum levels of IgG and IgA, normal or increased serum levels of IgM, negligible expression of CD40L by activated T cells, and CD40L gene mutation (Table 1). Expression of CD3, CD4, and CD8 by peripheral blood T cells, CD19 and CD40 by B cells, and CD56 by NK cells were within age-matched normal control ranges (data not shown). All these patients developed NEC as a likely complication of XHIGM.

Demographics and clinical courses of NEC

Case 1 was born to nonconsanguineous Hungarian parents (Table 2). He was first hospitalized at 11 months of age with interstitial pneumonia caused by *P. jirovecii*. After successful treatment of the pulmonary disease with tripethoprim-sulfamethoxazole (TMX) and intensive care he developed prolonged neutropenia with absolute neutrophil count (ANC) of less than 0.5×10^9/l. Recombinant human granulocyte colony-stimulating factor (rhG-CSF) therapy resulted in sustained elevation of ANC to physiologic range. Over the second and third years of life he developed several episodes of respiratory and gastrointestinal tract infections, and chronic diarrhea. At 4 years of age he required hospitalization and treatment with metronidazole for pseudomembranous colitis. After the diagnosis of XHIGM was confirmed, monthly intravenous immunoglobulin (IVIG) substitution was started at a dose of 400mg/kg resulting in markedly reduced number of infections and he remained clinically stable. Bone marrow transplantation (BMT) could not be performed because of the lack of matched related donor (MRD) or matched unrelated donor. At age 7 he presented with loss of appetite and weight, severe diarrhea and abdominal distension. CT scan revealed an enlarged liver with multiple focal lesions, and enlargement of mesenterial lymph nodes (Figs. 1a, b). Histological analysis of the liver biopsy specimen suggested undifferentiated NEC (Figs. 1c–f). Treatment with octreotide, etoposide, and cisplatin did not result in any improvement and he died of hepatic insufficiency and cerebral edema 1 week after admission. At autopsy a yellowish-red tumor measuring 8mm in diameter was found in the head of the pancreas. The hepatic foci infiltrated the majority of the liver parenchyma, and tumors were found in the large intestine. Routine histological and immunohistochemical analysis showed that the pancreatic tumor was composed of undifferentiated cells, with a positive staining for chromogranin A, and a strong CD56 positivity (Figs. 1e, f). Based on the current WHO classification the tumor was classified as a poorly differentiated small cell NEC.

Case 2 was born to unrelated German parents (Table 2). At 3 months of age he developed pneumonia caused by *P. jirovecii* and required artificial ventilation and high dose therapy with TMX. After the diagnosis of XHIGM was made he was commenced on IVIG replacement therapy at 400mg/kg monthly. In addition, he received rhG-CSF therapy until the age of 5 years for recurrent neutropenia. Subsequently, his history was uneventful for almost a decade apart from a growing obesity. He discontinued cotrimoxasole prophylaxis without contracting another episode of *P. jirovecii* infection and he also deferred BMT despite the availability of a MRD.

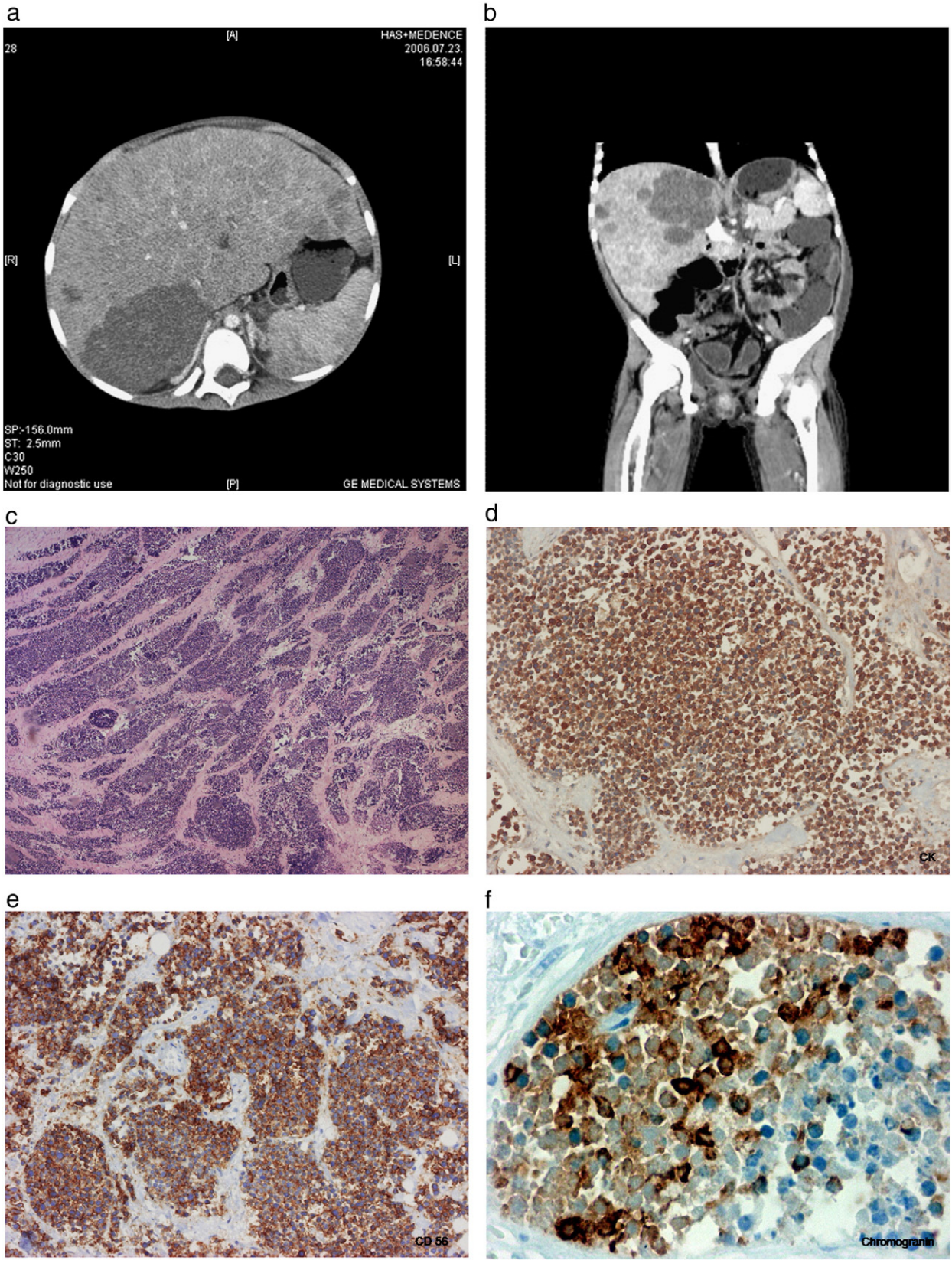
At age 14 he presented with diarrhea and recurrent abdominal pain. Ultrasound revealed multiple lesions of low echogenicity in the liver (Fig. 2a). Positron emission tomography (PET) revealed multiple lesions in the head of the pancreas. Liver biopsy unveiled a malignant small cell tumor with neuroendocrine and epithelial differentiation, and 90% of undifferentiated cells of the tumor expressed CD56. Therapy was introduced with oxiplatin, irinotecane, and gemcitabine of 7 courses, and with iphosphamide,

Table 2 Patients with neuroendocrine carcinoma associated with XHIGM

Case *N°*	Ethnicity (Nationality)	Diagnosis of XHIGM	Diagnosis of NEC	Affected organs	Chemotherapy regiments	Survival after diagnosis of NEC	References
1	Caucasian (Hungarian)	4 yr	7 yr	Pancreas, liver, ileum, lymph nodes	Octreotide, etoposide, cisplatin	7 d	This report
2	Caucasian (German)	4 yr	14 yr	Pancreas, liver	Oxiplatin, irinotecan, gemcitabine, iphosphamide, vincristine, actinomycine D	Alive	This report
3	Caucasian (German)	3 yr	14 yr	Pancreas, liver, os ilium, lung, lymph nodes	VIDE	6 wk	This report
4	Caucasian (Austrian)	9 yr	16 yr	Pancreas, liver	VIDE	8 yr	This report
5	American	?	21 yr	Pancreas, liver	Irinotecan, cisplatin	1 yr	[11]
6	Israeli	8 m	22 yr	Left colon, omentum	Bleomycine, etoposide, cisplatin	15 mo	[10]
7*	NK	NK	10 yr	Pancreas (glucagonoma)	NK	NK	[5]
8*	NK	NK	22 yr	Liver, omentum,	NK	NK	[5]
9*	NK	NK	24 yr	Duodenum, liver, lymph nodes	NK	NK	[5]

XHIGM, X-linked hyper-immunoglobulin M syndrome; NEC, neuroendocrine carcinoma; VIDE, *V*incristine-*I*-phosphamide-*D*oxorubicine-*E*toposide; yr, year; mo, month; wk, week; d, day; NK, not known;*Case IDs in Ref. 5 are QH (Case 7), FY (Case 8), and GS (Case 9).

vincristine, and actinomycin for 3 courses. The therapy was complicated by cholestasis requiring percutaneous transhepatic biliary drainage. After completion of chemotherapy, MRI of the liver showed regression of the lesions and PET scans showed no active lesions. Due to the bleak outcome of the tumor and the availability of a MRD, BMT was performed at age 15½. The transplant showed normal course of engraftment but 6 months after BMT the liver lesions



increased in size and number. Waiting for deterioration due to this apparently NEC relapse the patient withdrew from medical care and did not attend further follow up visits. Surprisingly, however, he is still alive and is stable 18 months after BMT. Whether the functional transplanted immune system was able to delay the progress or even reverse the course of NEC remains to be elucidated.

Case 3 was born to unrelated German parents (Table 2). His mother and 10-year-old brother are healthy, and his father died 8 years ago at age 35 of cancer involving the liver. During the third year of life he required medical attention for recurrent febrile infections of the respiratory tract. None of these infections took a particularly severe course but because of the frequency and of failure to thrive he was evaluated for suspected immunodeficiency. After the diagnosis of XHIGM was made, monthly IVIG substitution was started with a dose of 250mg/kg, which resulted in significant improvement of his clinical condition. As infections rarefied the parents refused BMT. At age 14 he presented with weight loss, malaise, and a large abdominal mass at a local hospital where liver biopsy was performed. The tumor was initially diagnosed as Ewing sarcoma and the patient was referred to the University Hospital Ulm. On admission, he was cachectic, looked severely ill and was unable to stand without help. The huge abdominal swelling was caused mainly by the enlarged liver extending down to the pelvis and causing intense abdominal pain. MRI showed a liver size of 23 × 12 × 25cm with multiple metastases up to 7 × 6 × 7cm, enlarged abdominal lymph nodes, and a pancreas destructed by tumor masses (Figs. 2b, c). PET and CT unveiled abdominal tumor with multiple metastases to the liver, lung, abdominal lymph nodes and the os ilium. Histology studies showed tumor tissue consisting of medium-sized cells which were arranged in rosettes. The cores were oval-shaped and hyperchromatic. The tumor was strongly positive for cytokeratin, synaptophysin, and CD56. The initial chemotherapy consisted of vincristine, iphosphamide, doxorubicin and etoposide (VIDE). A good initial response was observed with significant reduction of tumor size and pain, and improvement of general condition and liver function, and a second VIDE block was performed. However, no further response was achieved and a rapid tumor progression was observed and the parents decided on palliative treatment and the patient died 6 weeks later.

Case 4 was born to healthy unrelated Austrian parents (Table 2). He had one healthy brother and one older brother died of *P. jirovecii* pneumonia at the age of 3. At the age of 4 months he was hospitalized with interstitial pneumonia and was successfully treated with TMX and gentamycin. At the age of 8 he developed pneumonia caused by *Mycoplasma pneumoniae,* and over the following years he had several episodes of *Herpes simplex* skin infections. After the diagnosis of XHIGM was confirmed, regular immunoglobulin infusions (150mg/kg/month) and TMX prophylaxis was started. At 16 years of age he presented with jaundice, abdominal pain and pancreatitis (serum amylase, 931U/L; lipase, 7570U/L). Radiological examinations showed a small tumor in the area of the Oddi's sphincter. Octreotide scan showed multiple tumors in the liver. Percutaneous liver biopsy was performed and histology suggested the diagnosis of atypical Ewing sarcoma. He received five courses of VIDE in reduced intensity. Due to the multiple liver metastases tumor resection "*in toto*" was not possible and a cadaveric liver transplantation was performed. Immunosuppression with mycophenolat, cyclosporine, and methylprednisolone was commenced and he remained stable for 3 months. In hope of a graft versus tumor effect and to treat the combined immunodeficiency, allogeneic bone marrow transplantation was performed. The post-transplantation period was uneventful for 3 months and there were no signs of graft versus host disease or graft rejection. Three months later, however, he developed a recalcitrant invasive pulmonal aspergillosis and died at age of 17.

Discussion

PID patients are at risk for developing cancer predominantly of lymphoreticular origin such as lymphoma and leukemia. Ataxia telangiectasia, the Wiskott–Aldrich syndrome, and common variable immunodeficiency are the most common immunodeficiency syndromes predisposing patients to cancer; different mechanisms may be responsible for the association of PID with malignant diseases. Ataxia telangiectasia predisposes patients to develop lymphoid malignancies due to chromosome instability and translocation involving chromosomes 12 and 14 [14]. The most frequent malignancy that has been reported in association with the Wiskott–Aldrich syndrome was lymphoma with Epstein–Barr virus positive B cells suggesting viral etiology [15]. The increased risk for gastric cancer in patients with common variable immunodeficiency and other forms of hypogammaglobulinemia may be related to chronic infection with and impaired elimination of *Helicobacter pylori* from the gastric mucosa [16]. Our observation, in keeping with the known susceptibility of PID patients to malignancies in general, provides strong evidence of the unique association of XHIGM with NEC, in particular, and indicates a high susceptibility of CD40L-deficient patients to develop this type of tumor.

Patients with XHIGM often develop chronic cholangiopathy and cirrhosis which may predispose them for liver and biliary tract tumors [4–6]. That XHIGM patients may develop NEC was first reported by Hayward et al. [5]. Our report of four new patients and retrospective analysis of five published cases suggest that NEC may be more common in XHIGM than in any other PID. Data of this study and that of

Figure 1 Horizontal abdominal CT scan and microscopic images of the tumor of Case 1. (a) Horizontal abdominal CT scan revealed an 84 × 64mm mass in segment 6 of the liver which compressed the inferior caval vein. (b) Transversal abdominal CT scan showed multiple liver lesions of tumor origin. The dilated intestine and a significant amount of free intra-abdominal transudation are visible. (c) Poorly differentiated infiltrating tumorous nests that replace the pancreas are indicated by plain arrows (H and E stain, magnification, × 40. (d) By immunohistochemical analysis the tumor cells show strong cytokeratin expression (magnification, × 100). (e) The neuroendocrine tumor showed a strong CD56 positivity (magnification, × 100). (f) Most of the tumor cells display positive reaction for chromogranin *A* (magnification, × 400).

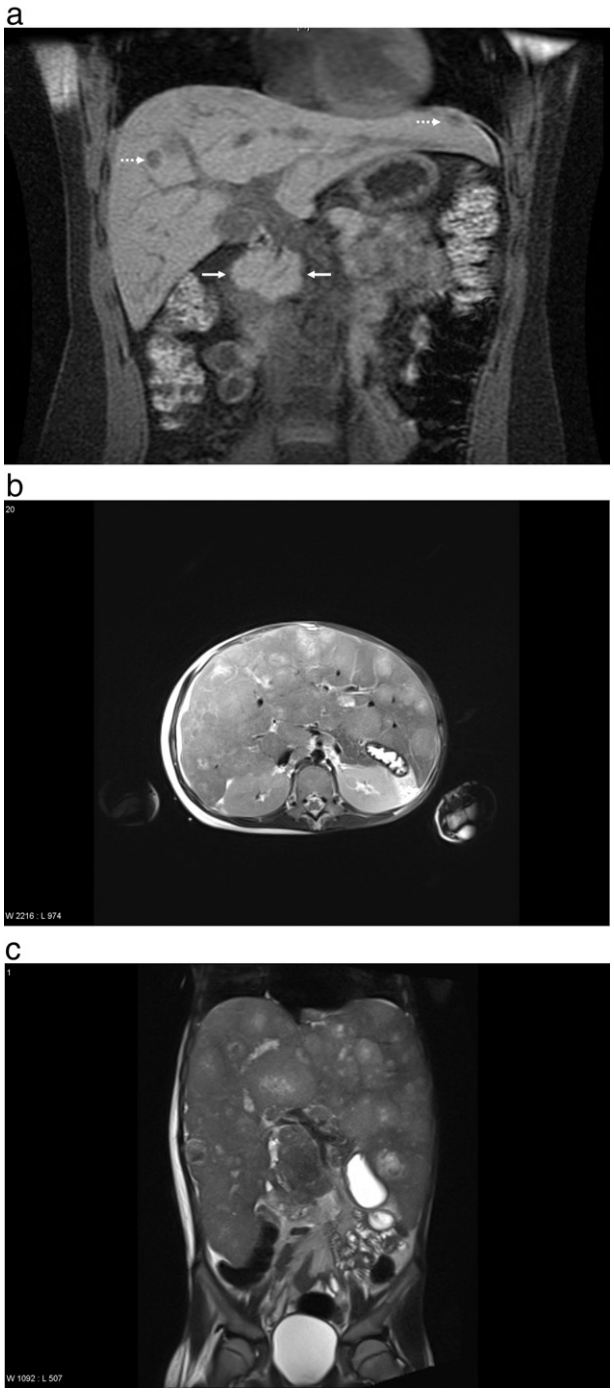


Figure 2 Abdominal MRI sections of Cases 2 and 3. (a) Coronal MRI section of the abdomen of Case 2 at the time of diagnosis of NEC. Note the inhomogeneous mass at the head of the pancreas (plain arrows) with hyperintensity in T2 weight and enhancement by dimeglumingadopentetat contrast medium (Magnevist). Also note the hypodensic hepatic lesions (dotted arrows). (b and c) Horizontal and frontal MRI scan of Case 3. The scans show a huge abdominal mass that involves the liver and the spleen. In large parts, the borders of liver and spleen are not recognizable.

previous reports suggest that NEC may develop in childhood but it may be more frequent in adolescents and young adults with the classic XHIGM phenotype. The average age at diagnosis of NEC was 16.5years (range, 7 to 24 years) suggesting that the incidence of this cancer increases as XHIGM patients get older.

NEC has a poor prognosis illustrated by the fact that all but one of the 6 patients with available disease outcome data died (Table 2). In all of our four patients and in Case 5 the pancreas and the liver were involved and gastrointestinal symptoms were present. NEC developed as a rapidly disseminated cancer in our patients and it was so huge at diagnosis that it was impossible to recognize the primary site. The occurrence of cancer cells in different organs at the same time is possible but we have no evidence for this.

The neuroendocrine origin of the tumors was evidenced by immunohistochemical methods. It has been well established that neuroendocrine carcinomas express cytokeratin and chromogranin A in the vast majority of cases. CD56 has also been shown to be overexpressed in several nonhemopoetic malignancies mainly in neuroendocrine tumors and in adenocarcinomas with neuroendocrine differentiation [17]. Our findings in Cases 1, 2, and 3 suggest that CD56 overexpression may be a useful marker to define NEC.

BMT is an approved treatment for patients with XHIGM, but none of our cases was transplanted as a primary attempt to cure the disease. The total number of patients registered currently with XHIGM in he ESID Registry is 85 out of 6965 total, which can be regarded as a minimum prevalence number. Surprisingly, only 17 of these registered XHIGM patients were treated with BMT ([12]; B. Gathman, personal communication). This may be related to the wide heterogeneity of the severity of XHIGM, a possible reason for not using BMT in the majority of patients even if donors are available. In addition, transplants are mostly done from matched related or unrelated donors who are not always available. Furthermore, refusal attitude of the families, as described here, may also add to the inappropriate management of XHIGM patients. BMT was used in Cases 2 and 4 after the development of NEC and one of these patients (Case 2) is still alive. This patient may have benefited from BMT even after developing NEC. After the diagnosis of XHIGM was made regular IVIG replacement therapy was started which resulted in significant clinical improvement in all patients. IVIG replacement decreased the frequency and severity of infections even in Case 4, who received suboptimal doses. One conclusion that can be drawn from this study is that counseling is critically important and the parents should be aware that BMT is the primary treatment of patients with CD40L deficiency.

In sum, we propose here that CD40L deficiency may be one specific risk factor predisposing patients for the development of NEC. The poor outcome of NEC in XHIGM patients characterized by impaired humoral and cellular immunity may be attributed to the severe defect of the immune surveillance. The precise mechanism by which patients with CD40L deficiency developed NEC more commonly than patients with other PIDs remains to be elucidated. Whatever the mechanism is our observation suggests that patients with XHIGM should be carefully followed to detect NEC early. Importantly, BMT as a primary attempt to cure patients with XHIGM may prevent or prolong the development of NEC, and should be performed despite improvement of patients on IVIG substitution. In addition patients with XHIGM should avoid carcinogenic exposure which may increase the risk of cancer.

Acknowledgments

This work was supported by the Hungarian Research Fund OTKA T49017 to LM and OTKA PD 72445 to ME). We are grateful to Benjamin Gathman and the ESID Online Database network team for their help in identifying the PID cases with NEC, and to Luigi Notarangelo for helpful discussion.

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