Letter to the Editor

Generalised Pruritus and Elevated Levels of Immunoglobulin E Acting as Biomarkers of a Malignant Peritoneal Mesothelioma

Dear Editor,

Generalised pruritus can be the primary manifestation of a systemic disease, sometimes, a neoplasm. Malignant peritoneal mesothelioma (MPM) is a rare local aggressive tumour of the peritoneum with high mortality rate (median survival 6 to 12 months). There are difficulties in achieving a correct diagnosis[1] as neither clinical symptoms nor image findings are specific.

A 47-year-old woman, with no evidence of asbestos exposure, presented with severe paroxysmal and generalised itching attacks for a duration of 3 months. The itching attacks usually occurred 5 or 6 times daily lasting only a few minutes each time. There were no responses to emollient creams and antihistamines. Physical examination did not reveal anything unusual except for dermographism and lichenified skin, secondary to scratching.

Investigations revealed a normal blood cell count except for 11.9% eosinophils (normal values 0% to 7%) and a total count of 1250 eosinophils/mm^2, serum IgE level over 5000 UI/L (normal values <100 UI/L), Blastocystis hominis cysts in faeces and high levels of specific IgE to Anisakis simplex (2.81 KU/L with normal values <0.35). Other findings were all negative, including biochemical profile, protein electrophoresis, thyroid studies, C reactive protein, urine analysis and serology for hepatitis C virus, HIV and Echinococcus granulosum.

Stool exam for ova and parasites and serum IgE to Anisakis simplex are the routine tests in the assessment of itch without dermatological cause in our hospital. Since both of them were positive, they were initially considered to be the two most likely causes of the patient's symptoms. The patient was treated with paromomycin, followed a diet including fish frozen for more than 48 hours, and took different types of antihistamines simultaneously, with no resolution of symptoms.

Six months later, a value of serum IgE of 12.313 UI/L was noticed. Chest radiography was normal but abdominal echography showed ascites and a 3 cm mass in the right ovary. A toraco-abdomino-pelvic computed tomography (CT) scan revealed ascites and multiple small nodules implanted in the peritoneum with an increase in the thickness of the greater omentum (Fig. 1).

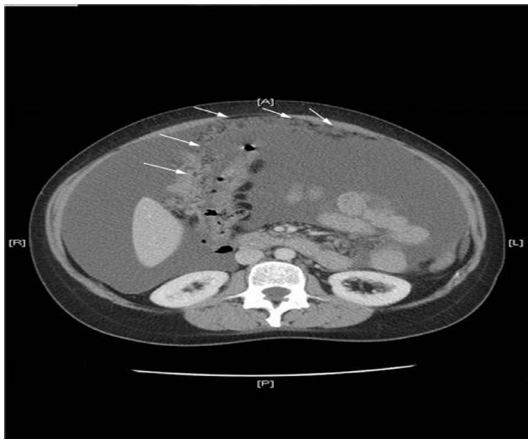


Fig.1. Abdominal CT scan revealed widespread small nodules on the greater epiplon (↑).

Diagnostic laparoscopy with double ooforectomy and salpingectomy, as well as omentum and peritoneal biopsies, were performed. Histopathological examination showed an omentum with extensive infiltration by epithelioid cells disposed in nests, cords and tubules, with globulous, irregular nucleus, lumpy cromatin and a small nucleolus; mitosis images were present. The nests had multiple lights filled with a blue acellular material, alcian-blue positive. Mesothelial surface was proliferated with papillae formation made of cubic cells and the same epithelioid cells previously described. These cells were positive for calretinin (diffuse), vimentin (focal), D2-40 (diffuse in the superficial mesothelial cells and focal in the infiltrating cells), CK-7 (focal in superficial mesothelial cells) and negative for caldesmon carcinoembrionary antigen, CK20, TTF-1, oestrogen and progesterone receptors. Both ovaries and fallopian tubes had superficial implants of neoplastic cells. The diagnosis of MPM was made.

She received systemic chemotherapy with 5 cycles of pemetrexed-cisplatin for 5 months. Then neoplasm was treated with cytoreductive surgery (complete peritonectomy and gall-bladder excision) and further intraperitoneal chemotherapy with doxorubicin and cisplatin. Evolution was satisfactory, without evidence of disease, with resolution of itching attacks and great reduction of IgE serum levels (IgE levels of 1825 UI/L and 1926 UI/L were detected 3 and 7 months later, respectively).

Fifteen months after the surgery, a CT abdomino-

pelvic scan revealed 3 new nodules in the left iliac fossa, perihepatic and perisplenic areas. IgE levels rose again to 9144 UI/L. A new laparotomy failed to resect the tumoral nodules, so again a combined chemotherapy with 8 cycles of pemetrexed-cispaltin was started. IgE levels fell to 1739 UI/L, 1570 UI/L and 809 UI/L, 2, 3 and 5 months after starting chemotherapy, respectively, with improvement in CT scan images.

The term 'paraneoplastic syndrome' is used to describe the indirect effects of cancer; secondary to the production of biologically active hormones, growth factors, and other yet unidentified substances; or secondary to tumour-induced antigen-antibody interactions that cross-react with epithelial antigens and cause skin involvement.[3] Paraneoplastic pruritus is most frequently observed in leukaemias and lymphomas. In Hodgkin's disease, the rate of pruritus is determined to be 1% to 11%.[4] Among the visceral neoplasias, it is not only most often seen in pancreas and stomach cancers, but also found to be associated with other tumours.

Increase in total serum IgE levels can be observed in many medical conditions,[2] from atopy to infection (parasitosis, HIV), primary immunodeficiency (Job's syndrome) and malignancy (Sézary syndrome, IgE multiple myeloma). Therefore, the total IgE level is neither a sensitive nor a specific diagnostic marker for any particular disease.

The link between IgE and cancer is still unknown. The most direct relationship occurs with IgE myeloma. Hodgkin's disease, especially the nodular sclerosis type and squamous cell carcinomas of the head and neck have also been associated, finding significant elevations of serum IgE levels in the group of patients with relapses.[5]

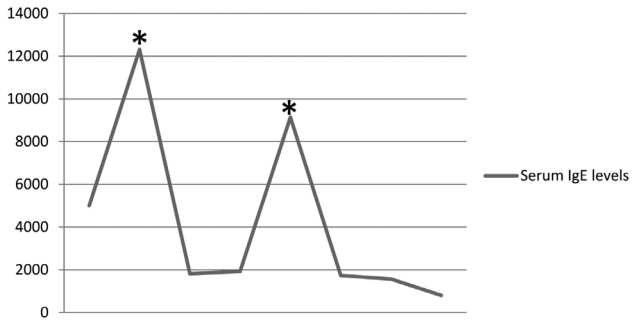
Another possible relationship between IgE and neoplasms involves tumour-specific IgE antibodies. A few studies suggest that IgE antibodies specific for tumour antigens are formed. Serum levels of IgE and its low-affinity receptor, soluble CD23 (sCD23) have been recently studied in patients with pancreatic cancer.[4] They were both elevated significantly in comparison to the controls. No differences were observed in other Ig isotypes (IgG, IgM, IgA). These data suggest that IgE may be an important biomarker for diagnostic or prognostic purposes. Moreover, sera obtained from these patients were able to mediate antibody-dependent cell-mediated cytotoxicity through IgE-specific antibodies to a pancreatic cancer antigen. In future, it may be useful in IgE-mediated therapy for cancer.

Our patient is still alive after 3 years of follow-up. As she has surpassed the median survival of MPM (6 to 12 months), we therefore think an antitumoral effect of IgE is plausible. We suggest an antibody-dependent cell-mediated cytotoxicity through IgE-specific antibodies to a MPM antigen. In this case, IgE has acted as a biomarker of the disease (Table 1). The last recorded value of serum IgE level was 809 UI/L, so we think that significant residual tumour is present although the actual clinical status of the patient is good.

To conclude, this case of MPM is exceptional because of the pruritus as the unique initial symptom during several months before the diagnosis, and the behaviour of serum IgE levels running a parallel course with the malignancy. More studies are necessary to establish the real diagnostic and prognostic value of serum IgE in MPM and other types of cancer.

Table 1. Course of Serum IgE Levels over Time (see text). (*) Realise Decrease After Surgery and Chemotherapy

Months	Immunoglobulin E (UI/I)
0	5000
6	12313
9	1825
16	1926
24	9144
26	1739
29	1570
34	809



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