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To be or not to be: a two years surveillance for a CA 19-9 persistent elevation before cancer diagnosis and bone metastases

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Background. CA 19-9 is an antigen expressed by several epithelial cells and currently used for the diagnosis and follow-up of gastrointestinal cancers. Even if a serum level > 1000 UI/ml has a specificity for pancreatic cancer of 99.8% its elevation is also reported in benign diseases. The pancreatic ductal adenocarcinoma is tipically aggressive and therefore shorter follow-up are expected to be found before diagnosis.
Case presentation. A 75-years-old female referred to us for evaluation of high level of serum CA 19-9 (558 UI/ml) observed for the first time one year before when she had also been undergone colonoscopy that have excluded neoplasms.
At the adimission she complained fatigue, weight loss, hyporexia, nausea, low-grade fever and intermittent self-limiting skin lesions of the lower limbs. Serum CA 19-9 level was > 1000 UI/ml.
Her past medical history was significant for chronic HCV hepatitis, essential hypertension and hysterectomy for leiomyofibroma of the uterus thirty years before.
We did not found any neoplasm and scheduled a close follow-up with colonoscopy, CT and PET for one additional year. At the end of December 2015 we observed the appearance of small painful nodules in the subcutaneous periumbilical region and a CT showed a pancreatic tail malignancy and bone metastases. Periumbilical biopsy was performed and the diagnosis of pancreatic ductal adenocarcinoma was proven.
Conclusion. A long time observation of a persistent and progressive CA 19-9 increase should never exclude the malignant origin. The trend, more than the duration of this finding may guide clinical decision.

Abbreviations
Carbohydrate Antigen 19-9 – CA 19-9
Computerized Tomography – CT
F-18-fluorodeoxyglucose positron emission tomography – 18F-FDG PET
Carcinoembryonic Antigen – CEA
Cancer antigen 125 – CA 125

Key words: Case report, CA 19-9, Pancreatic cancer, Tumoral markers, Bone metastases

BACKGROUND

Serum CA 19-9 is a carbohydrate antigen expressed by several epithelial cells and used for the diagnosis and follow-up of gastrointestinal cancers even if high serum level can be also found in several benign conditions [1]. Since pancreatic neoplasms are commonly very aggressive and rapidly progressive [2], CA 19-9 elevation immediately preceeds the diagnosis of the tumour.

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CASE PRESENTATION

A 75-years-old Caucasian woman referred to us in December 2014 because of fatigue, weight loss, hyporexia, nausea, low-grade fever and intermittent self-limiting skin lesions of the lower limbs together with persistent elevation of serum CA 19-9 level (> 1000 UI/ml) and piastrinopenia (90.000 cells/uL). BMI was 23 kg/m^2.
Her past medical history was significant for chronic HCV hepatitis, essential hypertension and hysterectomy for leiomyofibroma of the uterus thirty years before.
She said that one year before she had observed fecal blood and was undergone to colonoscopy that revealed two rectosigmoid polyps with focal high grade dysplasia on histological examination. At that time CA 19-9 was 558 UI/ml. Whole-body computed tomography (CT) did not find any solid lesions but only mild splenomegaly. A bone marrow examination showed no significant alterations. 18-F-fluorodeoxyglucose positron emission tomography (18F-FDG PET) ruled out neoplasms.
On physical examination the patient was pallid and very weak. Oedema and purpuric rash of the lower limbs were observed.
Blood count showed hemoglobin 8.2 g/dl and platelets 59000/uL and CA 19-9 was confirmed > 1000 UI/ml. Alphafetoprotein and carcinoembryonic antigen (CEA) were normal. Cancer antigen 125 (CA 125) was 145 UI/L (ULN < 35). Creatinine 109,1 umol/L (GFR 45 ml/min) and urea nitrogen 31,4 mmol/L. ESR was 35 mm/h. Liver function tests, prothrombin time and bilirubin were normal. Autoantibodies (ANA, AMA, ASMA, anti-LKM, c-ANCA, p-ANCA and anti-dsDNA) were negative. Serum C4 levels were markedly reduced (< 1.67 mg/dl) whereas C3 levels was normal. A cryoglobulinemia was suspected and a 5% cryocrit was demonstrated in the serum consistent with HCV-related mixed cryoglobulinemia.
Thyroid ultrasound, echocardiogram, pancolonoscopy were normal and whole body CT scan revealed liver cirrhosis and moderate splenomegaly associated with portal hypertension and sigmoid diverticula. No nodular lesions were found.
Prednisone 50 mg/daily was started with rapid improvement of clinical conditions and resolution of purpura.
Prednisone was tapered to 5 mg/daily and sofosbuvir plus ribavirin were introduced for HCV treatment with complete virological response obtained in 4 weeks.
A strict surveillance with blood tests and abdominal ultrasound was scheduled monthly and a CT scan was planned six month later. CA 19-9 levels remained persistently elevated > 1000 UI/ml but general conditions improved and no malignancies were found until September 2015 (Fig. 1) when an episode of abdominal periumbelical pain and hyporexia were reported.

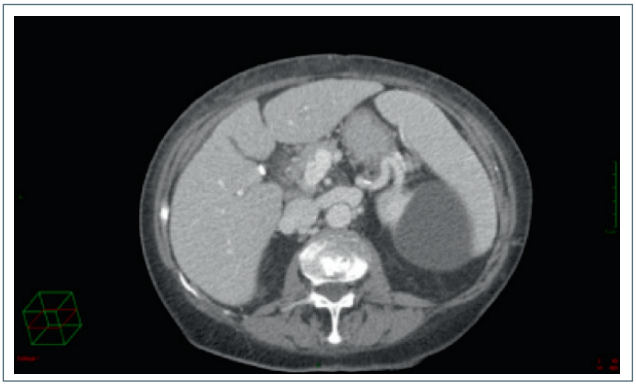

Figure 1. Abdominal CT scan – venous phase (first admission): no pancreatic lesions were observed.

In November 2015 small painful nodules in the subcutaneous periumbilical region were noted at the clinical examination. Serum CA 19-9 levels were > 10,000 UI/ml.
Abdominal ultrasound revealed multiple subcutaneous solid hypoechoic nodules with a poorly defined and irregular borders, irregular shape (Fig. 2).
Abdominal CT revealed a large lesion (4 cm) in the pancreatic tail consistent with pancreatic malignacy not observed in the previous scan (Fig. 3). Multiple nodules in the liver, subcutaneous layer of abdominal wall and rib metastases were also detected. 18F-FDG PET (Fig. 4) showed hypermetabolic activity of all lesions.
Periumbilical biopsy was performed and the diagnosis of metastatic pancreatic ductal adenocarcinoma was proven. The patient died two months later.

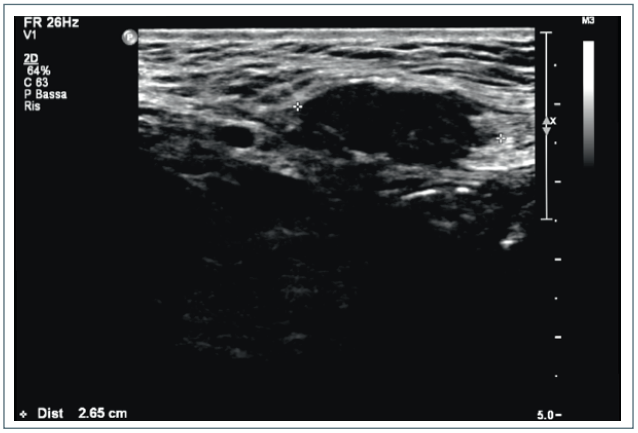

Figure 2. Abdominal ultrasound (November 2015): multiple subcutaneous solid hypoechoic nodules with a poorly defined and irregular borders and irregular shape were found out in abdominal wall (Linear probe – Philips IU22).

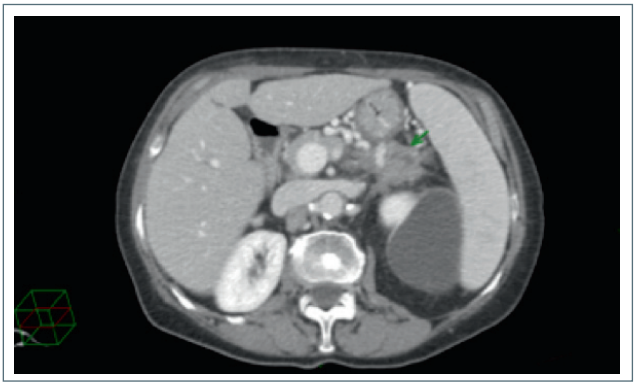

Figure 3. Abdominal CT scan – venous phase (November 2015): a large mass (4 cm) in the pancreatic tail is showed (green arrow).

DISCUSSION

CA 19-9 is the most used marker for the detection of gastrointestinal malignancies.
It was originally defined by a monoclonal antibody produced by murine spleen cells immunized with a human colorectal cancer cells [3 4].
Its name is derived from the monoclonal antibody called 1116-NS-19-9 directed against a carbohydrate epitope expressed on sialylated Lewis a antigen [5]. Therefore the Lewis blood type is pivotal for the synthesis of the marker and only patients expressing Le^{a+b-} or Le^{a-b+} genotype may produce CA 19-9.
About 5-10% of the population shows Lewis blood

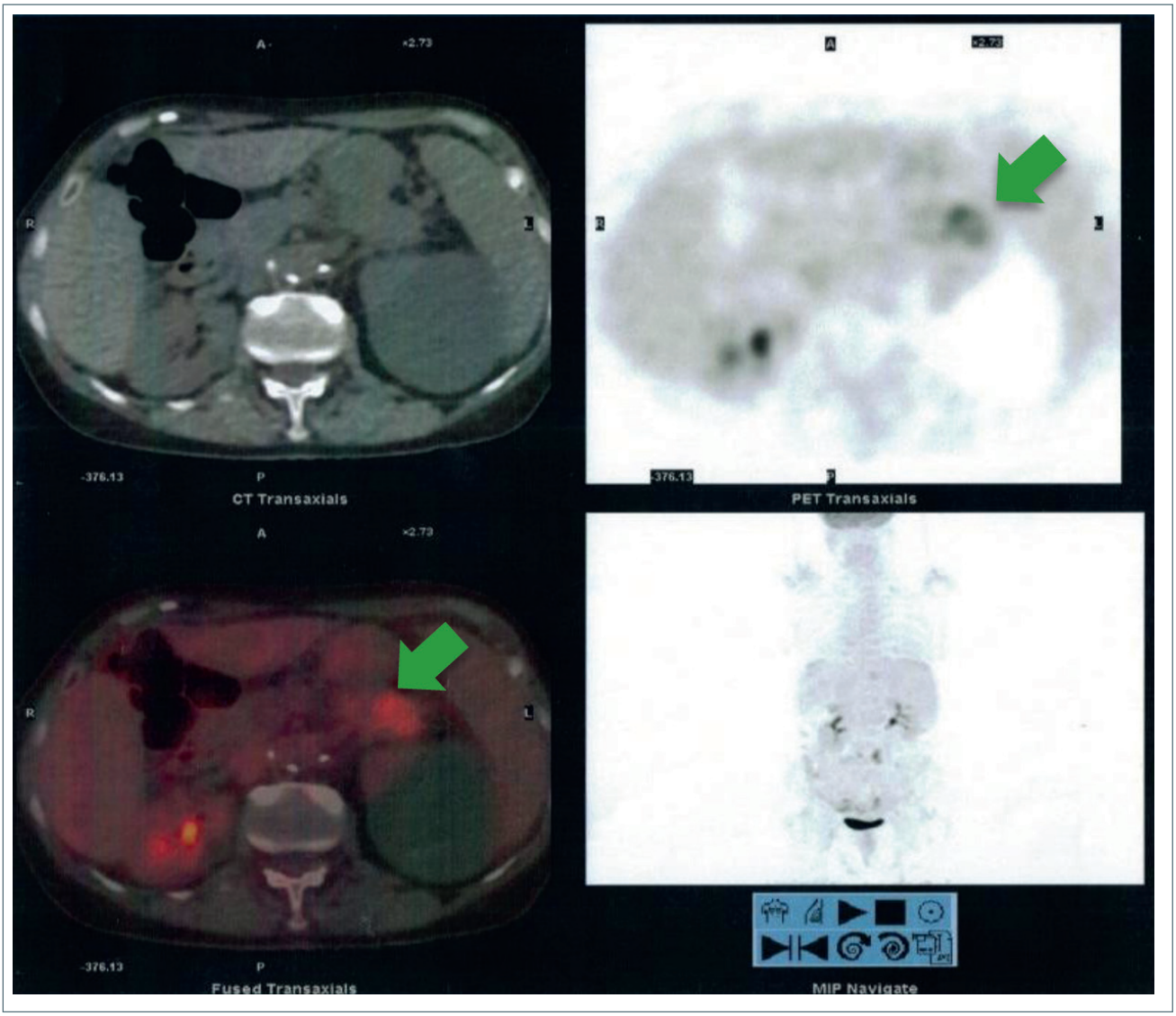

Figure 4. 18F-FDG PET (November 2015): the pancreatic lesion show hypermetabolic activity (green arrow).

type negative (Le^{a-b-}) and fails to express it even when a tumor is detectable [2-4 6].

In individuals expressing Lewis blood type, CA 19-9 is synthesized by normal human pancreatic, biliary ductular, gastric, colonic, endometrial and salivary epithelia and secreted into the blood, saliva, gastric and bile juice [1 7 8]. CA 19-9 is currently considered the best marker of pancreatic cancer [7 8] even if biliary, hepatocellular, gastric, colonic and non gastrointestinal cancers may increase the serum level to > 1000 IU/ml [7]. Moreover, several benign diseases such as obstructive jaundice, cholangitis, chronic liver diseases, acute and chronic pancreatitis, diabetes mellitus, interstitial pulmonary disease, endometriosis, hydronefrosis, splenic cysts, colon diverticulitis [1 9] may associate with moderate CA 19-9 elevation < 200 UI/ml [3].

Pancreatic cancer CA 19-9 specificity is 90% with the cut-off 37 UI/ml and increases at 98% with 100 UI/ml; by using 1000 UI/mL specificity reaches 99.8% [2].

We should also taken into account that in early and small pancreatic cancers (< 3 cm) the sensitivity is very low and only 50% of malignant lesions produces CA 19-9 with some poorly-differentiated pancreatic cancers that may not produce it anytime [2].

For all these reasons, elevated CA 19-9 level alone is not indicated for the diagnosis of pancreatic cancer but only as indicator of asyntomatic recurrence, in preoperative evaluation of patient for surgical interventions and in monitoring of response in patients with locally advanced or metastatic disease receiving chemotherapy or radioterapy [3].

However, a question is so far unsolved: how long should we maintain active surveillance before excluding a malignancy?

Some authors reported several cases of patients monitored for 2-6 years without detection of cancer [1]. Such patients showed a mean serum CA 19-9 level of 517 U/ml and most of them had no significant past history of cancer. On the contrary, pancreatic ductal adenocarcinoma is tipically aggressive and rapidly metastasizing with short-term survival ranging between 8-12 months in locally advanced stages and 5-8 months in metastatic disease [2 10 11].

Few weeks are commonly required for the diagnosis even when the lesions are located in the pancreatic tail. Accordingly, a long time of CA 19-9 elevation intrinsically excludes a malignant neoplasm.

Kim et al. observed 501 asymptomatic subjects with elevated CA 19-9 level for at least 6 months and concluded that CA 19-9 should not be used as a screening tool and that the trend of the tumor marker may be more important than the level itself [7].

In the present case, elevation of CA 19-9 came two years before a pancreatic solid lesion appeared and several comorbilities (chronic hepatitis, diabetes) other than bowel diseases (colon polyps) could have, almost in part, explained the marker elevation. Pancreatic cancer appeared suddenly and with exceptionally aggressive behaviour only two months after the last CT scan.

CONCLUSIONS

We report a two-years follow-up of a 75 years old woman with persistent elevation of CA 19-9 before the diagnosis of pancreatic adenocarcinoma was done.

A long time observation of a persistent and progressive CA 19-9 increase should never exclude the malignant origin. The trend, more than the duration of this finding, may guide clinical decision.

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