Severe eosinophilia associated with cholangiocarcinoma

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It is widely recognised that eosinophils are found in tumor infiltrates and that their mechanism of action is associated with particular symptoms and prognosis. However, the causes of and reasons for this process remain unclear, as does the exact mechanism by which it occurs. We report on the case of a 71-year-old woman with cholangiocellar carcinoma (CCC) with a marked eosinophilia. When the patient presented at the hospital, she said she was suffering from fatigue, depression, and pain. That triad of symptoms, indicative of peripheral eosinophilia (TABE, or tumor-associated blood eosinophilia) and tissue eosinophilia (TATE, or tumor-associated tissue eosinophilia), are recurrent in oncology. We also conducted a structured review of literature on eosinophilia associated with biliary tumors to try to answer 3 questions: Is eosinophilia (TABE or TATE) associated with solid tumors, with particular reference to the tumor of the bile duct? Is eosinophilia in biliary tumors associated with specific symptoms? Does eosinophilia (TABE or TATE) predict a specific prognosis?

Case presentation and summary

In May 2014, a 71-year-old woman was admitted to the hospital with a range of symptoms including fatigue, depression, and vague abdominal pain during the preceding 4 months.When first examined by the hematologist, she was presenting with subicterus. The patient's hepatic tests were altered (alanine transaminase [ALT], 58 U/L; alkaline phosphatase [ALP], 1308 U/L; gamma-glutamyl transferase [GGT], 2189 U/L), and marked leukocytosis with eosinophilia and neutrophilia were shown: white blood cell (WBC) count, 48490/mmc; neutrophils (N), 20850/mmc; monocytes (M), 4850/mmc; eosinophils (E), 18910/mmc; lymphocytes (L), 3880/mmc. As a result, she underwent abdominal ultrasound inspection in the the emergency department. The ultrasound showed multiple nodules hypoechoic on liver, a lesion of 6.75 cm (2.7 in) the pancreatic region (between the pancreatic body and head), swollen intrahepatic bile duct, especially the left duct, and multiple peripancreatic and perihepatic lymphadenopathy. The chest X-ray was negative for parenchymal lesions.

The patient said she had no family history of allergies, had not traveled to a foreign country, did not use or abuse drugs, and had not had any direct exposure to chemicals. She had essential hypertension and a smoking habit. In 1986, she developed 2 brain aneurysm ruptures for which she underwent brain surgery, which was complicated by cerebral ischemia with hemiparesis on both sides and aphasia. Afterward, notable improvements were recorded but always with aphasia. In 2010, she experienced progressive locomotor performance decline. The patient was taking therapy: ACE inhibitor, statin, cardioaspirin, prophylactic phenobarbitral, selegiline, and proton pump inhibitors.

The physical examination revealed subicterus and moderate abdominal tenderness in the patient, who was observant, but aphasic. Clinical laboratory outcomes confirmed severe leukocytosis with hypereosinophilia (WBC, 48820 cells/mmc; N, 20800/mmc; E, 0640/mmc; L, 2390/mmc; M, 4520/mmc; B 70/mmc); increased necrosis and stasis liver tests (ALT, 50 U/L; ALP, 1156 U/L; GGT, 1993 U/L); total bilirubin, 2.83 mg/dL; direct bilirubin (D-bil), 2.53 mg/dL; macrocytosis (MCV), 103 fL; a decrease in folate (7.9 nmol/L); an increase in prothromin time (PT, 1.6 sec); biological inflammatory syndrome (CRP, 73.3 mg/L); mild polyclonal increase in gamma globulins (19.5%); hyperferritemia (778 Ug/L); and increased IgE (306 U/ml). Tryptase examination was not performed. Other exams were either normal or negative: total complement activity tests (C3, C4), ANCA, ANA reflex, HIV, immuno-

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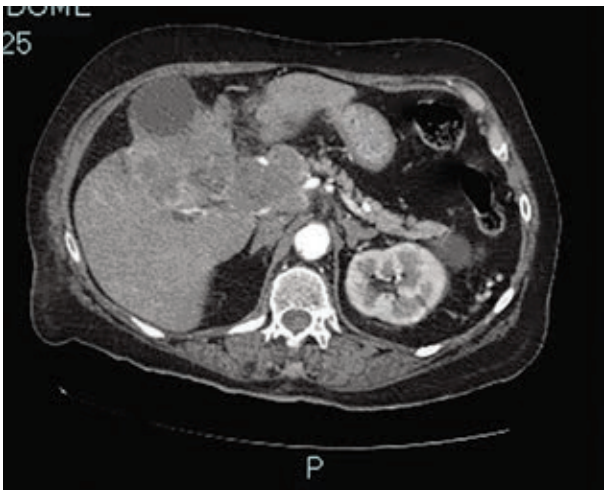

FIGURE 1 Abdomen contrast-enhanced computed-tomography scan.

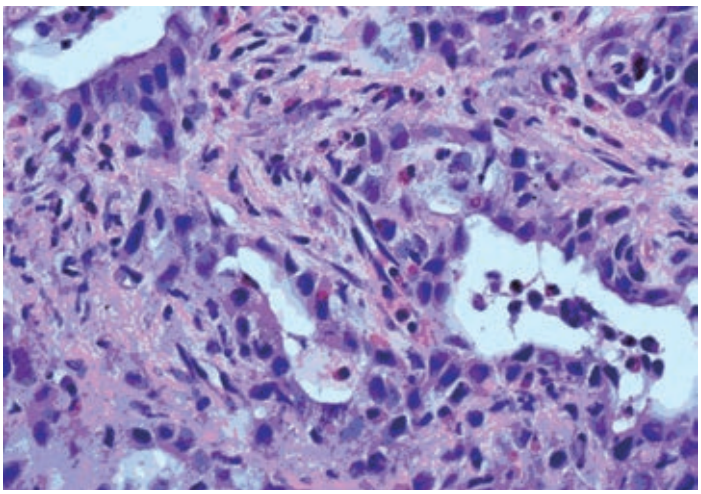

FIGURE 2 A liver histologic test showing malignant epithelial proliferation with areas of necrosis and stroma collagen and tissue eosinophilia (TATE).

globulis, Bence Jones in the urines, systemic IgG, and subclasses. Stool culture for fecal parasites was negative.

We first took into account a differential diagnosis of secondary eosinophilia, which are extensive and include allergic diseases, drug-induced eosinophilias, hematologic disorders, neoplastic disorders, and parasitic infections (mainly helminthes). Then we developed the following diagnostic hypotheses: CCC with liver metastases and secondary eosinophilia, pancreatic cancer with secondary eosinophilia, primary sclerosing cholangitis (PSC) associated with eosinophilia, hypereosinophilic syndrome affecting the bile duct, secondary sclerosing cholangitis (IgG4-related autoimmune pancreatitis associated with sclerosing cholangitis, intraductual lithiasis hepatic inflammatory pseudotumor, AIDS-related cholangiopathy), parasites (fluke, opsithorchiasis, and clonorchiasis).

A contrast-enhanced computed-tomography (CT) scan of the abdomen and thorax showed multiple confluent hepatic lesions (relative sparing of VI, VII, VIII segments); a lesion (58 x 39 mm [2.28 x 1.53 in.]) in the hilar and cefalopancreatic region, which was not separable, displaced the vascular structures, and compressed the vein and the common hepatic artery; and mild dilatation of the intrahepatic bile duct (Figure 1). The findings were interpreted as compatible with CCC or primitive neoplasm of pancreatic head with liver metastases.

A CT scan of the brain showed chronic vascular encephalopathy and the results of an electrocardiogram (ECG) test were normal. In the end, the radiological appearance suggested a CCC. However, there were other possibilities. First, the high eosinophilia count left open the possibility of a diagnosis for parasitosis, as detected through serologic tests. Our patient had not travelled outside of Italy, therefore she did not undergo any of those tests able to detect the parasites inhabiting in the tissue and blood. Second, administration of prednisone (40 mg/day) was instated for treating a presumed hypereosinophilic syndrome (HES). Indeed, HES (defined by an eosinophil count >1500 cells/mm^3, the absence of apparent causes for eosinophilia, and organ system damage) and chronic eosinophilic leukemia (CEL), a term used when there is a clonal population, are malignancies characterised by sustained idiopathic hypereosinophilia, which most commonly tend to affect the heart, skin, and nervous system through eosinophilis infiltration. Typically HES is not likely to involve liver and bilary tracts, however, cholecystitis chronic, hepatitis, and sclerosing eosinophilic cholangitis had been found and described, so we could not rule out a HES.

Primary sclerosing cholangitis does not respond to prednisone (except variant IgG4, but Ig subtypes were normal) as happened in our case.

We performed a biopsy of the left liver. The histologic test revealed malignant epithelial proliferation with areas of necrosis and extensive areas of stroma collagen: atypical cells forming glandular structures, simple and complex papillae and focal solid areas with widespread mitosis. Extensive stroma and tumor eosinophilic infiltrates were identified in the lesion area. Parenchyma and periportal spaces were also present. Immunohistochemitry showed strong and widespread positivity in proliferating cells for cytokeratin 7 and 19 and moderate for CDX2, focal positivity for cytokeratin 20 and thyroid transcription factor-1 (TTF1). The proliferation index was 65%.

These findings were interpreted to be compatible with moderately or poorly differentiated CCC with eosinophils found in large parts of tissue (Figure 2).

Because of the patient's declining condition, we did not perform echocardiogram tests. The bone marow biopsy, which is a mandatory examination to rule out the hematological malignancy, which was highly suspected because of the high

TABLE Selected studies with cholangiocellular carcinoma and eosinophilia

Study (type)	Summation
Steel[1] (prospective observational)	
Participants: N, sex, age, race/ethnicity	N = 206; 72% men, 28% women; average age, 64 y (22-90); 91% white, 2% black, 6% Asian
Presentation	Pain 59%; asthenia 85%; anxiety and depression 70% Cluster I (asymptomatic: minor pain, fatigue, depression) 40%; Cluster II (symptomatic: high pain, fatigue, depression) 25%: Cluster III (asthenia: low levels of pain and fatigue, depression remarkable) 35%
Diagnosis	Hepatocellular neoplasia 84%; cholangiocarcinoma 5%; neuroendocrine 3%; gallbladder 6%; liver metastases 6%
Investigation	Functional Assessment, liver functioning tests, immune system parameters
TABE/TATE	TABE is associated with pain, fatigue, depression (F (1,78) = 3,1; *P* = .05) at 3-6 mo follow-up, and is associated with increased survival in patients with or without vascular invasion.
Management	Not specified
Histology	Not specified
Prognosis/follow-up	TABE is associated with increased survival in patients with and without vascular invasion.
Conclusions, confounding bias	High levels of pain, fatigue and depression were found to be associated with elevated eosinophil percentage at 3- and 6-mo follow-up. Pain was the primary symptom associated with TABE between diagnosis and 6 mo. TABE is associated with increased survival in patients with and without vascular invasion. Symptom clusters did not mediate the relationship between eosinophils and survival. *Confounding bias* Comorbidity, different forms of tumors of the liver and biliary tract
Seki[2] (short communication)	
Participants: N, sex, age, race/ethnicity	1 man, 55 y Not specified
Presentation	High fever and epigastralgia 1 mo before presentation
Diagnosis	cholangiocellular carcinoma, multiple myeloma
Investigation	Antigens of Fasciola hepatica and Toxocara canis, serum IgE, test for echinococcus infection, transcutaneal needle liver biopsy
TABE/TATE	TABE: marked leukocytosis with eosinophilia (26.3 x 10^3/microL: E 20%); TATE: no
Management	Chemotherapy with carboplatin and fluoruracil via hepatic artery infusion
Histology	Bone marrow aspiration: hypercellular marrow with proliferation of eosinophils to 21.6% and plasma cells to 10%. On autopsy: cholangiocellular carcinoma (moderately to poorly differentiated tubular adenocarcinoma) massively occupied the whole liver. Cancer metastasis in the lymph nodes of the peripancreatic and retroperitoneal regions and in the sternum. Multiple myelomoa IgA lambda in moderately cellular marrow with osteolytic mass formation.
Prognosis/follow-up	Patient died of bone marrow suppression and pulmonary bleeding 3 mo after presentation.
Conclusions, confounding bias	Eosinophilia is not associated with a good prognosis. *Confounding bias* Major comorbidity
Mir-Madjlessi[3] (case report)	
Participants: N, sex, age, race/ethnicity	1 man, 26 y Black
Presentation	Itching and jaundice
Diagnosis	Mild to moderate, extensive ulcerative colitis for at least 3 y (marked eosinophilia and laboratory evidence of hepatic disease compatible with pericholangitis). Subsequently diagnosed with sclerosing cholangitis and bile duct carcinoma. Metastasis: adrenal glands, pericardium, left lung, abdominal and mediastinal lymphnodes.
Investigation	Percutaneous liver biopsy, ERCP, abdomen CT scan
TABE/TATE	TABE: 1 y before WBC 11600/mm^3, 56% eosinophils, WBC 11700/mm^3, 41%-23% eosinophils. TATE: pleomorphic portal infiltration with marked eosinophilia 1 y before.
Management	Cholecystectomy and external transhepatic drainage of the right hepatic duct, then 2 courses of 5-FU

Continued on p. 176

TABLE /continued from p. 175

Histology	Moderately differentiated adenocarcinoma of bile duct and dense periductal fibrosis on biopsy specimen. On autopsy, mucin-producing, poorly differentiated adenocarcinoma of the bile duct.
Prognosis/follow-up	The patient died from pulmonary embolism after 2 y.
Conclusions, confounding bias	TABE is not associated with a good prognosis. *Confounding bias* Hypereosinophilic syndromes could not also be ruled out.
Ohtsuki[4] (case series)	
Participants: N, sex, age, race/ethnicity	N = 4; 3 women aged 53, 55, 67 y; 1 man, 67 y Japanese
Presentation	Not specified
Diagnosis	Gallbladder adenocarcinoma
Investigation	Histopathological exam of resected gallbladder, hepatic parenchym, hepatic bed, extrahepatic bile duct
TABE/TATE	If the interval between the first operation (cholecystectomy) and second operation (resection of hepatic bed and extrahepatic bile duct) is 1 week, no granuloma formation with eosinophil accumulation (TATE) was detected. If the interval was more than 2 weeks, the resected hepatic bed contained necrotizing granulomas with eosinophil accumulation combined with an increase in peripheral eosinophilia (TABE) – up to 34% in 1 case.
Management	Cholecystectomy
Histology	Gallbladder adenocarcinoma
Prognosis/follow-up	Not specified
Conclusions, limitations	Clinicians and pathologists should keep in mind that the phenomenon of eosinophilic infiltration around necrotizing granulomatous changes associated with eosinophilia can occur. Further investigation is required to identify the real cause of eosinophil accumulation and eosinophilia. *Limitations* Only histopathological study of the surgical piece

CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; 5-FU, fluorouracil; TABE, marked peripheral eosinophilia; TATE, marked tissue eosinophilia; WBC, white blood cell

levels of total WBC (about 50000/mmc), could have been not performed because of the patient's rapid decline. However, the rapid progression to death may be considered secondary to the course of a hematological disease rather than that of a CCA, whereby on the contrary, the levels of function liver tests (FLTs) did not foresee such a dramatic evolution. Moreover, serum ALP levels, which were markedly elevated in this case, can be increased in several haematological malignancies

Discussion

We conducted an extensive and systematic research in PubMed using the mesh term *eosinophilia*, *bile duct tumors*, *eosinophilia,* and *cholangiocarcinoma*. The filters were *adults*, *English*, *human beings,* and the date range was January 1, 1985 to July 23, 2014. That search yielded 3 case reports and cases series and an observational prospective study.[1-4] Two cases were excluded because they were not presented in English,[5,6] as were cases that presented eosinophilia related to parasitic infections (Table).[7-9]

Cluster symptoms, such as fatigue, depression, and pain, and eosinophilia in bile duct tumors are strongly linked.[1] On average, 3 or more symptoms have been found and linked to each other.[10-14] Among the selected studies that we examined, the observational study of large series[1] is characterized by this triad of recurrent symptoms in oncological disorders. By contrast, in the other cases[2,3] and the observational study of large series,[4] only pain is present.

In this regard, the National Cancer Institute has stated that fatigue, depression, and pain are the most common symptoms and the most undertreated symptoms in patients with cancer.[15] The symptoms are present in 25% of patients with hepatobiliary cancer, and by 6 months after the diagnosis of cancer, the cluster is recorded in 62%-85% of cases reference.[1] Finally, in the larger observational studies, high levels of pain, fatigue and depression, high levels of eosinophilis were observed during the first 3-6 months of follow-up in patients with cancer.[1]

Study findings have suggested that the 3 symptoms can indicate an underlying biological mechanism.[1,11,14,16,17] Numerous elements seem to be involved in the immunological model (cytokine IL-3, IL-5, GM CSF secretion of IL-1, IFN-gamma, IL-2, IL-6, monoamine metabolism, ACTH resistance to glucocorticoid receptors, L-trypotophan reduction). Indeed, eosinophils are frequently observed in immunotherapy with IL-2, IL-4, IL-9, granulo-cytemacrophage colony-stimulating factor, and antibody to CTLA-4 16.

Our case was characterized by the presence of TABE and TATE, but poor prognosis, as with the 2 cases we cite,[2,3] which also showed a poor prognosis, although there was no prognosis in the case series.[4] By contrast, in the large observa-

tional study,[1] TABE showed a noticeable positive prognosis for patients with hepatobiliary carcinoma, although TATE and TABE can be observed independently and TABE was frequently observed in metastatic and advanced diseases.

The literature fails to provide an adequate answer to these questions and remains vague and inconsistent. The mechanism of the recruitment of eosinophils into the tissue of tumors also remains unclear.[16] On the one hand, it has been suggested that eosinophils regulate tumor necrosis (through cytokine pattern, immune response, vascular permeability and muscle contraction, toxic granules releases).[17] Typically, eosinophils are strongly linked to necrotic areas and the cytotoxic affect caused by eosinophils on tumor cells in vitro and in vivo is undeniable. On the other hand, the increased activation of eosinophils in allergic patients and in some eosinophilia-associated diseases can perform both a destructive/exacerbating and reparatory role.[16] In addition, tumor-associated eosinophils perform at least 2 unrelated functions.[16,17] The first is a destructive function, whereby they are potentially limiting the tumor growth and stimulate the recruitment/activation of other leukocytes. Indeed, the concept of TABE- and TATE-promoted innovations in the treatment of cancers and the execution of TABE after the therapy seems to be associated with a better prognosis in solid tumors. The first of such therapies include kinase inhibitors, imatinib, sorafenib. The second function is immunoregulative or remodelling, whereby they suppress the immune response and cause the tumor proliferation.

Some studies[16,17] have clearly shown an improved prognosis with TATE regardless of the degree of vascular invasion (or evidence of eosinophils degranulation) in various types of solid tumors. These include colon tumors, oral squamous cell carcinoma, esophageal squamous cell carcinoma, nasopharyngeal carcinoma, penile cancer, laryngeal carcinoma, pulmonary adenocarcinoma, bladder carcinoma prostate cancer. This beneficial influence of eosinophil in tumors activity seem to be independent from other common (standard) factors such as degree of progression, age, sex, alcohol and tobacco consumption, histologic grading, vascularisation, vascular invasion and neural invasion. These findings need further research to investigate whether there is or not a correlation or a mere association.

On the other hand, TATE is highly associated with poor prognosis in other tumors such as Hodgkin lymphoma, which is frequently characterised by a tumor mass consisting of an inflammatory infiltrate suggesting immune deregulation by this B-cell tumor. Often, TABE and TATE occur in carcinomas mucino secernentes (intestine, pancreas, bronchi, uterus) where they indicate and widespread tumor and metastases. In the end, the reports on solid tumors, such as oral SCC or cervical carcinoma, suggest that TATE is an indicator of poor prognosis.[17] The role of hypereosinophilia in malignant disease remains obscure, but first of all, certainly among the various causes of hypereosinophilia, clinicians should consider the presence of a solid and hematological tumor. Answering the 3 questions posed at the outset of this report (p. 173) could be a good starting point for developing prognostic criteria.

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