Potential role of parasitosis in tumorigenesis: Case study of heart metastasis as the only presenting symptom of an ileal neuroendocrine tumor

Une parasitose peut-elle être impliquée dans la tumorigénèse ? À propos d’un cas de métastase cardiaque unique révélatrice d’une tumeur neuroendocrine iléale

Case report

A 56-year-old male patient with an unremarkable medical history, other than a 40-pack-year history of cigarette smoking stopped one year earlier, was hospitalized for chest pain that had occurred over the previous 2 days, radiating to the jaw and both upper extremities. The electrocardiogram showed non-specific repolarization disorder, and the laboratory test results a slightly high troponin level, moderate leukocytosis and increased CRP (C-reactive protein) of 174 mg/L (normal < 6). The diagnosis of myopericarditis was considered; however, trans-thoracic echocardiogram found an infiltrating homogenous tissue-like mass, with little vascularization, measuring 35 mm. Cardiac CT scan (figure 1A) clarified its localization at the postero-inferior part of the interatrial septum, limited to the exterior by the pericardium and displacing the inferior vena cava and the postero-inferior part of the atria. Cardiac MRI confirmed a T1-hyposignal lesion with circumferential gadolinium contrast uptake. The cardiac valves were normal. An abdominal CT scan, used for investigating other tumor locations, revealed two mesenteric adenopathies, 1 cm in size. Surgical excision of the cardiac mass was performed. The pathology findings on the surgical specimen concluded that it was a well-differentiated neuroendocrine tumor, 45 mm in size, which had positive immunohistochemical staining for anti-cytokeratin, anti-chromogranin A and anti-synaptophysin antibodies (figure 2). The Ki-67 labelling index was 4%. It was probably a secondary location, since primary cardiac neuroendocrine tumors have exceptionally been described (2 cases reported). Scintigraphy of somatostatin receptors (Octreoscan®) was normal, but 18F-FDG positron emission tomography (PET), which has a better sensitivity, showed a high ileal uptake (figure 1B). CT enterography confirmed the presence of a 15 mm ileal endoluminal lesion associated with centimetre-sized adenopathies, with no liver lesions found on CT, MRI, Octreoscan® or FDG-PET. Levels of neuroendocrine tumor biomarkers were increased in the blood but not in urine (table 1). The patient had a right ileocectomy in which a 15 mm lesion was removed; this was found to be a well-differentiated neuroendocrine carcinoma extending from the submucosal to the subserosal layers and associated with four lymph node metastases. Tumor proliferation expressed in the same manner as anti-chromogranin A and anti-synaptophysin antibody metastasis. The Ki-67 labelling index was 8.7%, with a mitotic index of 18 at the highest power field. Liver biopsy showed no metastasis. In conclusion, this was a neuroendocrine tumor that was grade G2 (according to the 2010 WHO classification) and stage pT3N1M1 according to the 7th edition of the 2007 TNM and ENETS classification.

Of note was the fortuitous discovery, during the macroscopic exam of the surgical specimen, of a parasite in the small intestine, Taenia saginata (figure 3). An anti-secretory and anti-tumor treatment with lanreotide was started as first line treatment after multidisciplinary consultation. Re-evaluation after 12 months of treatment showed two images on FDOPA PET, one costal (figure 1C) and the other parasternal. A third suspicious focal point appeared in the pararectal fossa, which could not however be confirmed after 2 fine needle aspiration attempts guided with endoscopic ultrasound (figure 1D). The treatment with lanreotide was increased, and diphosphonate treatment courses were started. Four years following diagnosis of his illness, the patient had no other symptoms, except for grade I diarrhoea.

Discussion

Intracardiac metastases are rare, despite an increasing incidence over the last 30 years. These cases of metastasis are usually asymptomatic, and are discovered during the initial work-up at a very advanced stage of the cancer, or on autopsy findings [1,2]. Cardiac metastasis was thus present in 1.5% to 21.3% autopsy series cases in patients with cancer. They were located in the myocardium in 42% of cases, the epicardium in 30%, the pericardium in 19% and the endocardium in less than 6%. Cardiac metastases are different from right-sided valvular heart disease that occurs when carcinoid tumour...
cells metastasize from a primary site in the gut to the liver so that vasoactive substances produced by the tumour are able to reach the systemic circulation. As in our case, the pericardial or epicardial position of the lesion often presents as pericardial pain, while in the myocardial position, patients are asymptomatic or may present with conduction disorders. Some primary tumors have high cardiac metastatic potential (lung, breast, melanoma, lymphoma, leukemia, and thymoma); others have nearly no cardiac metastatic potential (e.g. prostate, thyroid, liver) [1]. $^{18}$FDG, $^{68}$Ga somatostatin receptor or DOTANOC PET/CT enables detection of these rare sites of metastasis [3–5]. Neuroendocrine tumors rarely produce heart metastasis, with less than 50 cases reported in the literature. The incidence of heart metastasis from neuroendocrine tumors is about 4% [6]. These metastases are most often detected by transthoracic echocardiogram during monitoring of carcinoid heart disease once they become greater than 1 cm in size. The most
frequently encountered primary neuroendocrine tumors are by far intestinal tumors, particularly in the ileum [6,7]. This is consistent with the case that we are reporting here, with the particular feature of heart metastasis as the presenting symptom. It should be noted that despite their low frequency, Merkel cell tumors (primary cutaneous neuroendocrine tumors) account for 12% of reported cases (4 published cases) [8]. As with other types of cancer, neuroendocrine tumor heart metastasis is generally synonymous with advanced disease, and patients very frequently already have liver involvement. In our case, there was no other secondary involvement at the time of diagnosis. After 4 years of follow-up, the patient still had no liver lesions. The patient was treated with a somatostatin analog for its anti-tumor effect, as an alternative to therapeutic abstention for neuroendocrine tumor with weak metastatic volume tumor, as recommended by ENETS 2012 [9].

Less than 5 similar cases of heart metastasis without liver metastasis have been identified in the literature. The primary disease involved ileal, appendicular and pancreatic neuroendocrine tumors [10–12]. The authors made no hypothesis as to the existence of secondary cardiac lesions in the absence of hepatic lesions; this situation was in contrast to the hypothesis of dissemination through blood vessel via the portal system, which is traditionally accepted for these tumors of digestive origin. In the case of the appendicular tumor [11], the patient was an excessive alcohol drinker and had hepatic Hodgkin’s lymphoma found on autopsy. These diseases can promote the development of collateral venous circulation, which might then explain the presence of heart metastasis in the absence of secondary hepatic lesions.

In the literature, only two cases of primary cardiac gastrinoma have been reported [13,14]. Given the rarity of primary cardiac neuroendocrine tumor, a metastatic localization has to be first eliminated. The case that we report on was particular due to its association with gastrointestinal parasitosis. Over the past few years, several parasites have been identified as carcinogenic by the International Agency for Research on Cancer (IARC). An example is the case of 3 trematodes that belong to the family of flatworms: Schistosoma haematobium, Opisthorchis viverrini and Clonorchis sinensis. The carcinogenic mechanisms remain poorly understood but involve chronic inflammation, immune modulatory effects, and inhibition of intracellular communication [15]. In the case of the 3 trematodes, oxidative stress and endogen nitrosation induced by inflammatory cells could have result in free radicals excess, leading to DNA strand breaks and pro-oncogene mutations [15]. Interleukin 7 (IL-7), a cytokine involved in lymphocyte recruitment, might also play an essential role at the crossroads of these different mechanisms [16,17]. A lack of IL-7 is the cause of severe congenital immune disorders: polymorphisms of its receptor, IL7Rα, alter susceptibility to certain autoimmune diseases; genetic mutations that activate this same receptor contribute to the neoplastic transformation of B and T lymphocytes [18]. Finally, IL-7 has been involved in some parasitic diseases (schistosomiasis, as well as malaria, leishmaniasis, toxoplasmosis, etc.) [19]. One study also showed its role in the cardiac dissemination of Chagas disease, a disease linked to Trypanosoma cruzi. In this case, the local production of IL-7 and other cytokines could have led to

**Table 1**

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<th>Evolution of neuroendocrine biomarker</th>
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<tr>
<td>Normal</td>
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<td>Chromogranine A</td>
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<td>Serotonin platelets</td>
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<td>5-HIAA</td>
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NSE: neuron specific enolase; 5-HIAA: 5-hydroxy indole acetic acid.
the selection of a population of CD8+ T lymphocytes, causing alterations in heart tissue [20].

The specific role of taeniasis was studied by Del Brutto et al. who observed that 16.8% of patients with a glome were infected by a neurocysticercosis, which is the larval stage of T. solium [21]. They suggested this infection might be a risk factor for developing a glome. Similarly, an experimental study has shown that the larval stage of T. taeniaeformis, Cysticercus fasciolaris, caused fibrosarcomas in rat liver [22]. Nevertheless, these hypotheses have never been confirmed, even if recent data suggest that a CD20 homolog expressed by tumor-associated macrophages and enhancing tumor growth could be induced by parasite infection [23,24]. To date, adult form of taeniasis, and therefore, T. saginata are not considered to be direct carcinogenic agents. Nevertheless, modifications of innate immunity and chronic inflammation induced by the presence of this parasite could have contributed to the particular dissemination of the neuroendocrine tumor.

To conclude, the reported case illustrates the possibility that a neuroendocrine tumor can present as an isolated heart metastasis without liver metastasis. This rare secondary location can present as an isolated heart metastasis from an appendiceal neuroendocrine tumor without liver metastasis.

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Disclosure of interest: the authors declare that they have no conflicts of interest concerning this article.

References