

SHORT REPORT

Bowel parasitosis and neuroendocrine tumours of the appendix. A report from the Italian TREP project

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SUMMARY

Five children with a neuroendocrine tumour (NET) of the appendix associated with a parasitic bowel infection are described, and the possibility of inflammation-triggered carcinogenesis is discussed. *Schistosoma haematobium* is linked primarily to bladder cancer but it has been reported in association with several other histotypes, including NETs of the gastrointestinal tract. Conversely, *Enterobius vermicularis* has not yet been claimed to participate in the onset of pre-cancerous conditions or tumours. The rare occurrence of contemporary appendiceal NETs and parasitic infection, raises the intriguing hypothesis of an inflammation-related carcinogenesis, although a cause–effect relationship cannot be established. Larger international series of childhood appendiceal NETs, which also include countries with higher prevalence of parasitic bowel infections, are needed to further clarify this possible cause–effect relationship.

Key words: Carcinoid tumours of the appendix, *Enterobius vermicularis*, helminths, neuroendocrine tumours, *Schistosoma haematobium*, TREP project.

Carcinoid tumours are rare, slow-growing tumours, arising from the enterochromaffin (Kulchitsky) cells disseminated throughout the gastrointestinal tract and bronchopulmonary system. Since 1980, the year of the first World Health Organization (WHO) classification of endocrine tumours, they have been classified as neuroendocrine tumours (NETs) [1].

These tumours are described more frequently in the bronchi and gastrointestinal tract, but can also occur at other sites, such as pancreas, thymus and ovaries. Although appendiceal NETs are rare in children and adolescents, they are nevertheless the most common gastrointestinal epithelial tumours in this age group and are usually an incidental finding after a laparotomy or laparoscopy for appendectomy. Several series have reported cases in children, but the precise incidence in relation to the total number of appendectomies is not available. The general incidence ranges between 1: 100 000 and 1·14:1 million children per year [2].

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In Italy, 113 appendiceal NETs in children have been registered in the TREP project database from January 2000 to May 2013. The TREP (Tumori Rari in Età Pediatrica = Rare Tumours in Childhood) project is a multi-institutional network dedicated to very rare tumours in children and adolescents [2, 3]. Among the patients registered, in five cases the tumour was associated with parasitic bowel infection, being *Schistosoma haematobium* in one case and *Enterobius vermicularis* in four cases.

A 15-year-old boy was admitted to the emergency department with abdominal pain, vomiting and fever. He had been living in Togo up to 2 months before admission. Blood tests and ultrasound (US) of the abdomen led to a diagnosis of acute appendicitis: the US also showed thickening of the bladder wall with a pseudo-polyp image. The boy underwent an open appendectomy from which he recovered uneventfully. In the immediate post-operative days he presented persistent haematuria, and it was established that this symptom had been present for the past 2 years, but no diagnostic investigation or treatment had been performed. As a urinary infection was suspected, another US scan of the bladder was performed together with parasite tests on urine samples. The urine tests confirmed the diagnosis of schistosomiasis and the patient was treated with oral praziquantel resulting in prompt resolution of the infection. The pathological report demonstrated a well differentiated NET (maximum diameter 5 mm), in the tip of the appendix, confined to the appendiceal wall, with worms and eggs of *S. haematobium* in the lumen. The diagnostic work-up for appendiceal NET, that includes Octreoscan, abdomen US, urinary 5-hydroxyindoleacetic acid (5-HIAA) and serum serotonin, was negative and the boy remains free from disease 40 months after diagnosis (Table 1).

Four girls, with a mean age of 10.5 years (range 7–13.5 years), with the clinical suspicion of appendicitis (fever, abdominal pain, emesis) underwent an emergency appendectomy. In all four cases, pathology reports showed a small NET associated with the presence of *E. vermicularis* eggs in the lumen of the appendix. All tumours were well differentiated, limited to the appendiceal wall and small in size (Table 1). The post-operative investigations for appendiceal NET (1/4 Octreoscan, 4/4 abdominal US, 4/4 urinary 5-HIAA +/- serum chromogranin or serum serotonin) resulted negative and all patients are alive and free from disease at a median of 35.5 months after diagnosis.

Schistosomiasis (or bilharziasis) is a tropical infection due to different trematodes belonging to the *Schistosoma* genus. The main schistosomes infecting humans are: *S. mansoni*, which causes intestinal and hepatic schistosomiasis in Africa, the Arabian peninsula and South America; *S. haematobium*, causing urinary schistosomiasis in Africa and the Arabian peninsula; and *S. japonicum*, causing intestinal and hepatosplenic schistosomiasis in China, Philippines, and Indonesia.

Appendicitis caused by *Schistosoma* spp. infection is a well recognized entity but rarely observed in Western countries. In the case of the 15-year-old boy presented here, the urinary schistosomiasis had been present for at least 2 years during the patient's time in Togo, and no diagnostic investigation or treatment had been performed until he came to our attention due to symptoms of acute appendicitis. The patient had never complained of abdominal discomfort previously, but it is known that in some cases, *S. haematobium* infection of the intestinal tract remain asymptomatic.

The International Agency for Research on Cancer (IARC) considers *S. haematobium* as a group 1 carcinogen (carcinogenic to humans) responsible for helminth-induced human cancer, and *S. japonicum* as a group 2b carcinogen (possibly carcinogenic to humans) [4]. Besides bladder cancer, in which schistosomiasis has a well-defined and proven carcinogenic role, other malignancies have been reported in association with schistosomiasis: these include colorectal carcinoma, lymphomas, hepatocellular carcinomas, rectal NETs and others [5].

Only four cases of appendiceal NETs associated with schistosomiasis have been reported so far [6–8], but none of these were in childhood.

The following sequence of events in schistosomiasis-induced carcinogenesis has been suggested: chronic infection leads to *Schistosoma* eggs becoming trapped in the organ wall; the constant irritation and subsequent inflammation associated with the secretion of particular parasite factors may determine carcinogenic initiation and progression [9]. The oncogenic potential of *S. haematobium* has been further investigated: nude mice exposed to Chinese hamster ovarian cells treated with *S. haematobium* antigens developed sarcomas, and normal epithelial cells treated with *S. haematobium* total antigen showed an increase in proliferation, migration, invasion and decreased apoptosis, with high-level expression of Bcl-2 [10]. It has been hypothesized that an oestradiol-related molecule

Table 1. *Clinical and pathological features*

Sex and age	Tumour size	Appendix inflammation	Grading*	Parasite	Symptoms†	Outcome (follow-up)
M, 15 years	0.5 cm	Yes	G1	<i>S. haematobium</i>	Haematuria	CR (40 mo.)
F, 7 years	0.2 cm	Yes	G1	<i>E. vermicularis</i>	None	CR (50 mo.)
F, 13 years	0.2 cm	Yes (chronic)	G1	<i>E. vermicularis</i>	None	CR (35 mo.)
F, 13.5 years	0.1 cm	Yes	G1	<i>E. vermicularis</i>	None	CR (36 mo.)
F, 8.5 years	0.5 cm	Yes	G1	<i>E. vermicularis</i>	None	CR (22 mo.)

CR, Complete remission; mo., month.

* According to WHO classification, 2010 [1].

† Other than appendicitis-related symptoms.

could be responsible for the carcinogenic effects, binding host DNA bases and acting as an endogenous initiator [11] in a recent study, Jiang and colleagues [8] demonstrated a higher expression of chromogranin A and Ki-67 in a series of three appendiceal goblet cell carcinoid tumours associated with schistosomiasis, indicating an increased cell proliferation and a neuroendocrine differentiation in mucosal crypt epithelium. These authors suggested that chronic schistosomal infection may contribute to the onset of goblet cell carcinoid tumours [8].

E. vermicularis is a nematode, also known as pinworm, the most common pathogen among helminths. It is transmitted via the faecal–oral route and affects 2–28% of children worldwide. The disease, secondary to *E. vermicularis*, is innocuous, with egg deposition causing perineal, perianal, and vaginal irritation; in the intestine the worms lie primarily in the caecum.

Although rare, appendicitis due to oxyuriasis infection has already been extensively described in the literature, but conversely *E. vermicularis* has not been linked to the onset of neoplastic disease: only two cases of concomitant appendiceal NETs and enterobiasis have been reported [12]. A cause–effect relationship between the co-existence of appendiceal NETs and *E. vermicularis* cannot be established, due to lack of biological and epidemiological data. However, some questions should be raised from these findings. Considering that the respective frequency rate of enterobiasis-related appendicitis and appendiceal NETs are both low in Western countries [13], is their concomitant manifestation only a coincidence? The rate of parasite-related appendicitis in the TREP database is 4.4%, slightly higher than that described in literature in Western countries (0.1–1.5%); however, on the other hand, paediatric *E. vermicularis* infections are very common and the true rate of parasite-related appendicitis may have been over-

looked in the past, both by pathologists and surgeons. Moreover, it is still unclear whether appendiceal NETs themselves could be a cause of appendicitis and appendiceal infestation by *E. vermicularis*, in these cases it may only be an incidental finding: this may add confusion to the situation considering the scarcity of cases reported in the literature, as in the case series presented here which is extremely rare.

Nevertheless, for *E. vermicularis* one might cautiously hypothesize a carcinogenic process triggered by chronic local inflammation caused by parasites themselves or their products, as seen in helminth- and trematode-related carcinogenesis [14, 15]: the small size and low grading of all four tumours in our series could be in keeping with a hypothetical inflammation-based carcinogenesis.

We have described five cases of NETs and concomitant appendiceal parasitic infections. Although only a few similar cases are described in literature and currently there is no proven causal link between *S. haematobium* and NETs of the gastrointestinal tract, the carcinogenic effect of *S. haematobium* is well known, and general evidence on the biochemical basis of tumour induction has been described recently. By contrast, the carcinogenic potential of *E. vermicularis* infection is less clear. This is the first report in the English language which theorizes a possible carcinogenic effect of oxyuriasis; however, to further confirm this hypothesis, more data, with a deeper analysis of larger series both in children and in adults, are needed.

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DECLARATION OF INTEREST

None.

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