Small bowel carcinoma revealing HNPCC syndrome

Carcinome de l’intestin grêle révélant un syndrome HNPCC

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Summary Small bowel adenocarcinoma is a rare condition with poor prognosis. Like colorectal cancer, small bowel carcinoma may be a part of genetic syndromes with carcinogenetic pathways different from sporadic forms. We report a case of 41-year-old man with small bowel carcinoma revealing hereditary non polyposis colorectal cancer (HNPCC) syndrome. This report supports the systematic study of the MSI status in every patient with a small bowel carcinoma below 60-year-old of age in order to screen for HNPCC syndrome even in the absence of a family history of related cancers.

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Introduction

Lynch’s syndrome or hereditary non polyposis colorectal cancer (HNPCC) syndrome is an autosomic dominant condition predisposing to multiple cancer occurring at a young age [1]. All cancers from the HNPCC spectrum may reveal this syndrome especially in the presence of a familial history of cancer [2].

We report a case of 41-year-old man presenting a small bowel adenocarcinoma (SBA) without known familial history of cancer. The identification of microsatellite instability associated with the absence of BRAF mutation strongly suggests the diagnosis of HNPCC syndrome, which was confirmed by the identification of a MLH1 mutation.

Case report

A 41-year-old man coming from India without known pathology was admitted in hospital for epigastric pain associated with vomiting and recent weight loss of 12 kg in the last 2 months. The clinical examination was normal and the blood test revealed iron deficiency anaemia. The upper gastrointestinal endoscopy demonstrates a tumoral mass of the junction between second and third segment of the duodenum. The anatomopathological examination of the biopsies revealed the diagnosis of adenocarcinoma. The CT scan
shows a thickening of the third duodenal without metastasis. A colonoscopy did not reveal synchronous colonic cancer or polyp. A partial duodenum resection was performed. The histopathology study of the resected specimen demonstrates an adenocarcinoma PT3N0M0 with perinervous involvement. An adjuvant chemotherapy with fluorouracil and folinic acid has been administered during 6 months after multidisciplinary decision. A test of microsatellite instability (MSI) phenotype was performed because of the young age of the patient. Four of the five microsatellites analysed (NR21, NR27, BAT25, BAT26) were instable, which indicates of the dysfunction of the mismatch repair system (Fig. 1). The V600 mutation of BRAF gene was absent, suggesting a possible hereditary origin of the mismatch repair (MMR) dysfunction. The immunohistochemical studies revealed extinction of expression of MLH1 protein (Fig. 2). The sequencing of MLH1 gene revealed a mutation of exon 9 (nt790+1 G > A). The familial screening was constrained because of the Indian origin of the patient. Nevertheless at least one coloscopy was performed in an uncle in India that revealed a colon tumour. After 4 years of follow-up the patient did not present any metachronous neoplasia.

Discussion

SBA is a rare tumour accounting for <2% of all gastrointestinal tumours [2,3]. The incidence of SBA is more frequent in some hereditary syndromes such as familial adenomatous polyposis (FAP), Peutz-Jeghers syndrome and HNPCC syndrome [4]. In the case of HNPCC syndrome the risk of developing SBA was estimated from 1 to 4% [5,6] with extreme from 1,3 to 7,2% [2,7—10]. The relative risk can be estimated as 200-fold as in the general population [2,5,6,11]. Nevertheless, we should mention that in previous study of 360 patients with MMR gene mutation, no case of SBA was identified [5].

In HNPCC syndrome, the age of occurrence varies between 39 and 52 years old as for colorectal cancer rather than 67 years old in sporadic SBA [2,11—13]. For SBA occurring in HNPCC a male predominance was observed with a sex ratio ranging between 2 to 3/1, while in colorectal cancers are equally distributed between man and woman [2,12—15]. In HNPCC duodenal primary are less frequent (36 to 45%) than in sporadic forms (46 to 56%) or than in of FAP [2,3,12,15,16]. In HNPCC syndrome, when SBA occur, it could revealed the syndrome in 34 to 78% [12,13,15,17—19].

A family history of cancer is not always available at diagnosis. Amsterdam I or II criteria are observed only in 50% of cases in a study of 31 patients with SBA associated with HNPCC [13]. Our patient didn’t have any familial history of cancer available only the young age conducted us to search for hereditary predisposing condition.

Microsatellite instability is observed in the majority of cases of SBA associated with HNPCC syndrome. Nevertheless, 5 to 20% of sporadic SBA have microsatellite instability.
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This frequency is similar to that observed in sporadic colorectal cancer. One previous study revealed that microsatellite instability is present in 23% of SBA occurring before age of 60 [4]. In our case the presence of microsatellite instability and the absence of the V600 mutation of BRAF gene conducted us to search for MMR gene mutation. In the case of HNPCC-associated SBA, there is a comparable frequency of HMLH1 and HMSH2 mutation whereas extradigester primary display a predominance of MSH2 mutation [2,4,19,24—26]. Rare cases of MSH6 and PMS2 were also reported [13,27].

SBA is a cancer of bad prognosis with the overall survival not acceding 30% at 5 years [2,28]. Clinical symptoms are frequently non-specific, which explains a late diagnosis not acceding 30% at 5 years [2,28]. Clinical symptoms like in colorectal cancers seems to be an independent prognostic factor [21]. The only curative treatment is surgery and the place of adjuvant chemotherapy is under evaluation. A French national cohort is now ongoing to evaluate SBA natural history and present therapeutic strategy in a large pane of patients (http://cohorte-engaine.com) [30]. In our patient, adjuvant chemotherapy was justified by the presence of the perinervous engagement like in colorectal cancer. The bad prognosis of this tumour is mainly due to late diagnosis. In HNPCC syndrome, a systemic screening of SBA is not recommended. Nevertheless the value of systematic enteroscopy or videocapsule endoscopy from age of 30 should be evaluated [13,15,31–35].

In conclusion, SBA is a rare cancer but it can be the first and the only manifestation of HNPCC syndrome even in the absence of known family history of cancer. Thus, in patient with SBA under 60, a systematic microsatellite instability screening should be performed and according to the result a search for MMR gene mutation.

Conflict of interest statement
The author has no conflict of interest.

References


