Small bowel carcinoma revealing HNPCC syndrome


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 associated with the absence of BRAF mutation strongly suggests the diagnosis of HNPCC syndrome, which was confirmed by the identification of a MLH1 mutation.
Figure 1  Microsatellite instability in the patient: for four of the five microsatellites studied (NR21, NR27, BAT25, BAT26), a shortened microsatellite marker is observed (indicated by a red dash) as well as the normal sized marker.

Figure 2  A. Immunohistochemistry with anti-MLH1 antibodies no nuclear staining in the tumoral tissue (NB, light cytoplasmic staining observed is not a criteria for positivity). Lymphocytes and macrophages of the stromal tissue present nuclear staining and are used as positive controls. B. Immunohistochemistry with anti-MSH2 antibodies MSH2: very clear MSH2 expression in the nucleus of tumoral cells.

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 PT3NOM0 with perinervous involvement. An adjuvant chemotherapy with fluorouracil and folonic 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

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 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].
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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 extradigestive 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 with T3 and T4 in the majority of cases [27,29]. The MSI status 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-nadege.com) [30]. In our patient, adjuvant chemotherapy was justified by the presence of the perinervous engainement 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 video capsule 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


