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Original contribution

Mismatch repair protein immunohistochemistry: a useful population screening strategy for Lynch syndrome

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Summary Lynch syndrome (LS), the most frequent form of hereditary colorectal cancer, shows a highly penetrant, autosomal dominant pattern of inheritance. Distinction of LS colorectal carcinoma instances from the much more common sporadic colorectal carcinoma cases is of paramount importance. Revised Bethesda Guidelines were developed to diagnose LS by evaluating a combination of clinical and pathologic data. The aim of the present study was to evaluate the usefulness of the pathology items included in the Revised Bethesda Guidelines. We have prospectively studied a series of 1624 consecutive colorectal carcinomas with an algorithm including immunohistochemical analysis of mismatch repair proteins and molecular study of microsatellite instability and *BRAF* c.1799 T > A (p.V600E) gene mutations. Patients with tumors showing LS features were referred for germline mutation analysis. By applying our algorithmic approach, we were able to identify LS features in 89 colorectal cancer patients, of whom only 27 met Revised Bethesda Guidelines pathology criteria. Of the 89 patients, 47 were then studied at the Genetic Counseling Unit, and LS was confirmed in 18, of whom 7 had not been identified by the Revised Bethesda Guidelines. Our study shows that the Revised Bethesda Guidelines failed to detect 70% of patients at risk of LS. Our algorithmic approach is a realistic and effective tool for LS identification. We strongly recommend the implementation of universal population screening for LS among all patients with newly diagnosed colorectal carcinoma.

1. Introduction

Lynch syndrome (LS), a highly penetrant, autosomal dominant cancer susceptibility condition, is the most frequent form of hereditary colorectal cancer (CRC) syndrome and accounts for approximately 5% of all CRCs [1]. Besides CRC, the spectrum of LS encompasses other primary tumors, some of which have been recently described [2,3]. Because LS is inherited as an autosomic dominant pattern, it is important to distinguish LS CRCs from the much more common sporadic CRCs. In addition, it is important to take into account that identification of an LS patient provides the opportunity to prevent neoplasms in other family members at risk of developing CRC or extracolonic cancers.

LS is caused by germline mutations in the mismatch repair (MMR) system genes, mainly *MLH1* and *MSH2* but also *MSH6* and *PMS2*. As a result, tumors that develop in an LS context characteristically show microsatellite instability (MSI). Recently, a new form of LS involving the epithelial cell adhesion molecule (*EPCAM*)/*TACSTD1EPCAM* gene has been described [4]. Of interest, CRCs with MSI often are

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poorly differentiated and frequently show mucinous or medullary histologic features.

A family pedigree including accurate data on malignant diseases is important to suspect the diagnosis of LS. Amsterdam criteria I and II as well as Bethesda Guidelines were developed to diagnose LS based on clinical features. However, it is a well known fact that cancer family history is a poor tool to identify LS patients [5,6]. Pathology items such as CRC histology were first taken into consideration when the Bethesda Guidelines were revised in 2004 [7]. Recently, study of all new CRC cases with immunohistochemistry (IHC) of MMR proteins and/or MSI analysis has been recommended to improve identification of LS patients [6]. The aim of the present study is to evaluate the usefulness of a newly developed diagnostic algorithm (mainly based on MMR protein IHC) for the identification of LS patients and to compare the efficiency of our screening approach with the results provided by the Revised Bethesda Guidelines.

2. Materials and methods

2.1. Cases

We prospectively studied a series of 1727 consecutive primary CRCs diagnosed at our institution between January 2005, and June 2012. Twenty-four CRCs were excluded because they were associated with polyposis. Of the 104 patients showing multiple tumors, 36 showed metachronous CRCs (M-CRCs), and 68 showed synchronous CRCs (S-CRCs). These multiple CRCs were studied in the same fashion as independent primary tumors. To simplify the algorithmic results obtained in M-CRCs, only the first tumor was taken into account in each case. As for S-CRCs, the neoplasm selected was the one with the higher stage. Finally, the series included 1624 prospectively studied CRCs belonged to 1624 patients with ages between 20 and 96 years (mean, 68.8 years; median age, 70.5 years). Of these, 974 (60%) were males and 650 (40%) were females.

2.2. Histopathologic features of tumors

Tumors were classified following the World Health Organization 2010 recommendations [8]. Mucinous adenocarcinoma showed mucin in more than 50% of the neoplasm, signet ring cell carcinoma required the presence of prominent intracytoplasmic mucin in more than 50% of tumor cells, and medullary carcinoma exhibited sheets of malignant cells with vesicular nuclei, prominent nucleoli, and abundant pink cytoplasm as well as prominent infiltration by intraepithelial lymphocytes (Fig. 1). Lymphocytic infiltration was considered to be present when a high density of intratumor lymphocytes (approximately 3 or more per high-power field) was identified in the tumor [9]. Tumor margin shape was expansive when the tumor front was well circumscribed or rounded, and it was considered to be infiltrative when the tumor front was predominantly irregular [10].

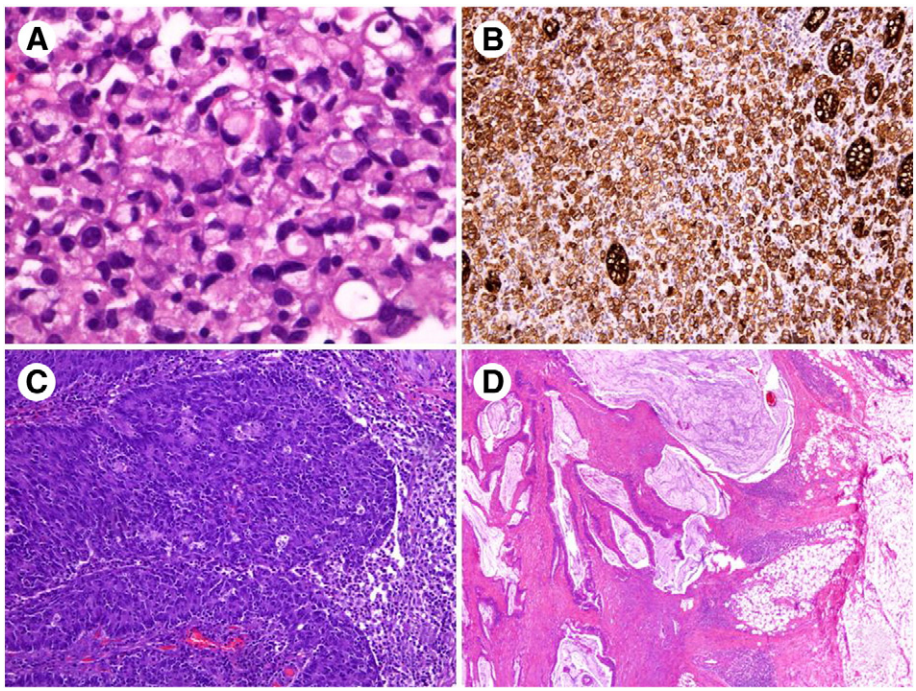

Fig. 1 Colorectal adenocarcinomas with Lynch phenotype. A, Signet ring cell carcinoma (hematoxylin and eosin). B, Signet ring cells with cytokeratin immunoexpression. C, Medullary carcinoma. D, Mucinous carcinoma.