and markers of antiphospholipid syndrome was negative. Renal biopsy was not performed due to severe anemia. The patient was given a diagnosis of ANCA-associated microscopic polyangiitis, rapidly progressive glomerulonephritis, and diffuse intra-alveolar hemorrhage that we attributed to D-penicillamine treatment. D-penicillamine was discontinued. Immunosuppressive treatment with three methylprednisolone daily pulses (750 mg/d), followed by 48 mg/d of methylprednisolone orally, and two cyclophosphamide pulses (10 mg/kg) alleviated hemoptysis and fever, reduced myeloperoxidase-ANCA and antinuclear factor titers, and increased hemoglobin level up to 101 g/L without erythrocyte transfusions. Nevertheless, kidney function did not recover. Cyclophosphamide administration was complicated by leukopenia, thrombocytopenia, and nosocomial pneumonia that resolved after antibiotics and intravenous immunoglobulin. We planned to start rituximab administration. However, the patient developed fatal respiratory infection within two weeks after discharge from the clinic.

Our findings suggest that serious immune-related adverse events are relatively infrequent in Wilson's disease patients receiving a long-term treatment with D-penicillamine. Nevertheless, D-penicillamine can induce a severe and even lethal ANCA-associated vasculitis with both rapidly progressive kidney failure and diffuse intraalveolar hemorrhage that requires discontinuation of D-penicillamine and immediate and aggressive immunosuppressive treatment.

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Conflict of interest

None declared.

Patient consent

Not required.

References

[1] Weiss KH, Thurik F, Gotthardt DN, Schäfer M, Teufel U, Wiegand F, et al. Efficacy and safety of oral chelators in treatment of patients with Wilson disease. Clin Gastroenterol Hepatol 2013;11(8):1028–35.
[2] Seessle J, Gotthardt DN, Schäfer M, Gohdes A, Pfeiffenberger J, Ferenci P, et al. Concomitant immune-related events in Wilson disease: implications for monitoring chelator therapy. J Inherit Metab Dis 2016;39:125–30.
[3] Sternlieb I, Bennet B, Scheinberg IH. D-Penicillamine-induced Goodpasture's syndrome in Wilson's disease. Ann Intern Med 1975;82:673–6.
[4] Bienaimé F, Clerbaux G, Plaisier E, et al. D-penicillamine-induced ANCA-associated crescentic glomerulonephritis in Wilson disease. Am J Kidney Dis 2007;50:821–5.
[5] Sharma R, Jain S, Kher V. ANCA-associated Goodpasture's syndrome in a patient with rheumatoid arthritis on penicillamine. Indian J Nephrol 2012;22:45–7.

Teona Rozina [a,b]
[a] *Tareev Clinic of Internal Diseases, Sechenov First Moscow State Medical University, Moscow, Russian Federation*
[b] *Faculty of Medicine, Lomonosov Moscow State University, Moscow, Russian Federation*

Saglara Fastovets [*]
Faculty of Medicine, Lomonosov Moscow State University, Moscow, Russian Federation

Olga Lee
Agunda Kuchieva
Nikolai Bulanov
Tareev Clinic of Internal Diseases, Sechenov First Moscow State Medical University, Moscow, Russian Federation

Sergey Moiseev [a,b]
[a] *Tareev Clinic of Internal Diseases, Sechenov First Moscow State Medical University, Moscow, Russian Federation*
[b] *Faculty of Medicine, Lomonosov Moscow State University, Moscow, Russian Federation*

[*] Corresponding author at: Tareev Clinic of Internal Diseases, Rossolimo, 11-5, Moscow, 119435, Russian Federation.
E-mail address: s.v.fastovets@gmail.com (S. Fastovets)

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Ready, get set, go: Fast preoperative genetic diagnosis is the present future in Lynch syndrome surgical strategy

Dear Editor,

Lynch syndrome (LS) is an autosomal dominant hereditary cancer predisposition syndrome caused by pathogenic germline variants in DNA mismatch repair genes (MMR) *MLH1*, *MSH2*, *MSH6* and *PMS2*. LS accounts for 3–5% of all colorectal cancers (CRC). LS associated CRC generally has microsatellite instability and lacks for MMR protein expression. The risk of CRC in LS patients is between 10 and 82% depending on the involved MMR gene. LS patients are at high risk to develop synchronous/metachronous cancer both colonic and extracolonic (e.g. endometrial, urothelial and ovarian) [1]. The risk of metachronous CRC is 62%, 30 years after surgery [2]. The optimal surgical treatment of CRC in LS is still debated. Extended resection, depending on clinical and molecular scenario, should be considered not only for primary CRC treatment but especially for prevention of metachronous CRC. Diagnosis for LS is molecular. However, germline genetic testing is performed postoperatively in the majority of cases, missing a possible important role in preoperative evaluation and surgical planning.

A 22-year-old female patient, after evidence of chronic anemia, was submitted to thorax-abdomen CT scan with evidence of a right colon neoplasm. Subsequent colonoscopy identified two lesions: a 8 cm stenosing neoplasm of the proximal portion of the right colon and a 3 cm sessile neoplasm in the caecum. The former was a moderately differentiated adenocarcinoma while the latter a tubulo-villous adenoma with focal areas of high-grade dysplasia. In the suspect of a LS, immunohistochemistry (IHC) testing for MMR was performed on the endoscopic biopsy with evidence of *MLH1* and *PMS2* protein lack of expression. Following genetic testing results were available within 7 days with identification of the pathogenic variant c.522_523dupGA (p.Lys175Argfs*28) in *MLH1*. After a detailed genetic and surgical counselling, the patient was submitted to laparoscopic total colectomy with ileo-rectal anastomosis. The neoplasm was a pT2 N0 Mx G3 adenocarcinoma. Discharge was on 6th postoperative day in optimal clinical conditions. Six months follow up was uneventful with a reported good quality of life.

Timing of LS diagnosis is critical in CRC patients because early diagnosis could guide the surgical strategy (extended versus segmental resection). However, diagnosis of LS is usually achieved postoperatively even a long time after surgery. Because LS accounts for 3–5% of CRC, IHC for MMR and/or microsatellite instability testing (MSI) are recommended in all CRCs [1]. Two studies

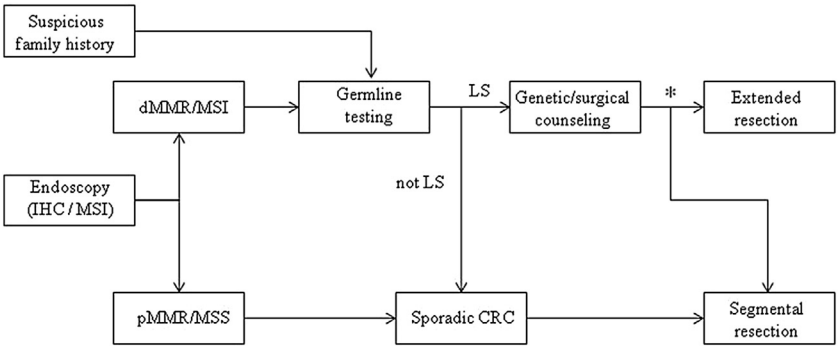

Fig. 1. Diagnosis and treatment algorithm. IHC: immunohistochemistry; MMR: DNA mismatch repair (MMR) genes; MSI: microsatellite instability testing; dMMR: defective MMR; pMMR: proficient MMR; CRC: colorectal cancer; LS: diagnosis of Lynch syndrome; *: factors influencing surgical strategy (age at diagnosis, comorbidities, MMR gene involve, history of adenomas, presence of synchronous colonic and/or extracolonic cancer, patient's choice).

have demonstrated that endoscopic biopsies are as reliable as the resection specimen in predicting MMR protein abnormality through IHC test [3,4]. However, several barriers to preoperative LS identification have been described [5].

In the past, germline testing was costly and time consuming and therefore not suitable on a preoperative schedule because of the risk of surgery delay. However, nowadays, new technologies make genetic testing faster (i.e. 7 days) and more affordable therefore opening the road to a potential novel diagnostic and therapeutic approach where the gastroenterologist acquires a fundamental role in early diagnosis of LS.

Routine IHC for MMR and/or MSI testing, together with accurate personal/family history collection, should be performed in every case of endoscopically detected CRC in order to obtain a preoperative LS identification and define the best surgical strategy.

In case of lack of familiarity on interpreting/applying the results of genetic testing and/or unavailability of an efficient genetic laboratory, the patient should be directed to referral centers.

Once LS is diagnosed preoperatively, a multidisciplinary counseling is mandatory in order to carefully discuss the possibility to perform an extended resection by considering several clinical factors (i.e. age at diagnosis, comorbidities, MMR gene involve, history of adenomas, presence of synchronous colonic and/or extracolonic cancer) and patient's choice. The algorithm for preoperative LS diagnosis and treatment, in patients with a novel diagnosis of CRC, is reported in Fig. 1.

It is time to overcome the past barriers and offer a preoperative LS diagnosis during CRC staging in order to guide the surgical strategy.

Consent

The patient has given his written consent.

Conflict of interest

None declared.

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References

[1] National Comprehensive Cancer Network. Genetic/familial high-risk assessment: colorectal (version 2.2019).
[2] Parry S, Win AK, Parry B, Kalady M, Macrae FA, Lindoret NM, et al. Metachronous colorectal cancer risk for mismatch repair gene mutation carriers: the advantage of more extensive colon surgery. Gut 2011;60(7):950–7.
[3] Shia J, Stadler Z, Weiser MR, Rentz M, Gonen M, Tang LH, et al. Immunohistochemical staining for DNA mismatch repair proteins in intestinal tract carcinoma: how reliable are biopsy samples? Am J Surg Pathol 2011;35(3):447–54.
[4] Kumarasinghe AP, de Boer B, Bateman AC, Kumarasinghe MP. DNA mismatch repair enzyme immunohistochemistry in colorectal cancer: a comparison of biopsy and resection material. Pathology 2010;42(5):414–20.
[5] Noll A, Parekh PJ, Zhou M, Weber TK, Ahnen D, Wu X, et al. Barriers to lynch syndrome testing and preoperative result availability in early-onset colorectal cancer: a national physician survey study. Clin Transl Gastroenterol 2018;9(9):185.

Guglielmo Niccolò Piozzi [1]
Colorectal Surgery Unit, Department of Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Maria Teresa Ricci [1]
Stefano Signoroni [*]
Unit of Hereditary Digestive Tract Tumours, Department of Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Marco Vitellaro [a,b]
[a] *Colorectal Surgery Unit, Department of Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*
[b] *Unit of Hereditary Digestive Tract Tumours, Department of Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

[*] Corresponding author.
E-mail address:
stefano.signoroni@istitutotumori.mi.it
(S. Signoroni)

[1] Guglielmo Niccolò Piozzi and Maria Teresa Ricci contributed equally as co-first authors.

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