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Rheumatoid Arthritis as a Therapeutic Challenge in a Patient with Lynch Syndrome

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Female, 63
Final Diagnosis: Lynch syndrome
Symptoms: —
Medication: —
Clinical Procedure: Medication adjustment
Specialty: Rheumatology

Objective: Unusual setting of medical care





Background: Lynch syndrome (LS) is an inherited colorectal cancer (CRC) syndrome accounting for about 3–5% of all cases and involves significantly higher risk of subsequent malignancies, colonic as well as extra-colonic. Increased risk of malignancies, especially lymphoid malignancies, have been described in patients with autoimmune diseases like rheumatoid arthritis (RA), systemic lupus erythematosus, and Sjögren's syndrome. Epidemiological studies demonstrated that hematopoietic, lung, skin, and prostate cancers are increased in RA, while breast and colon cancers are decreased, with an overall slight increase in all cancers.

Case Report: Our case demonstrates the development of CRC, endometrial cancer, and breast cancer as a presentation of LS in a patient with RA and presents a therapeutic challenge for RA treatment.

Conclusions: We describe a patient with LS and RA presenting a therapeutic challenge because biologic agents commonly used to treat severe RA need to be used cautiously in patients with history of malignancy.

MeSH Keywords: Arthritis, Rheumatoid • Biological Therapy • Lynch Syndrome II

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Background

Lynch syndrome (LS) is an inherited colorectal cancer (CRC) syndrome accounting for about 3–5% of all cases and involves significantly higher risk of subsequent malignancies, colonic as well as extra colonic. Among women, endometrial cancer is the second most common cancer associated with LS, with an estimated lifetime risk of 40–60%. Other associated malignancies of stomach, pancreato-biliary system, and small bowel have been described.

Increased risk of malignancies, especially lymphoid malignancies, have been described in patients with autoimmune diseases like rheumatoid arthritis (RA), systemic lupus erythematosus, and Sjögren's syndrome. Epidemiological studies demonstrated that hematopoietic, lung, skin, and prostate cancers are increased in RA, while breast and colon cancers are decreased, with an overall slight increase in all cancers.

Case Report

The patient was a 63-year-old woman with RA diagnosed in 2002 at Queens Hospital Center. She was initially started on hydroxychloroquine and methotrexate, followed by addition of adalimumab for active RA symptoms in late 2007 after discussing with proctology.

She was diagnosed with infiltrating adenocarcinoma of the recto-sigmoid s/p surgery in 1996, followed by chemoradiation and adjuvant chemotherapy completed in 1997. The patient had family history significant for cancer in many first-degree relatives. Her mother died from colon cancer at age 39 and her father died of lymphoma at age 64, her brother had colon cancer at age 32, a maternal cousin had colon cancer at age 62, a maternal uncle died of colon cancer at age 75, a maternal cousin died of pancreatic cancer, and 2 sisters have colon polyps requiring yearly colonoscopy.

In 2006, a colonoscopy showed a 3-cm flat mass lesion at the proximal transverse colon. Pathology revealed infiltrating adenocarcinoma for which she underwent right hemi-colectomy. She had subsequent follow-up colonoscopies. Following her surgery in 2006 periodic testing every 2–3 years has shown negative results for any tumor recurrence. In 2009 the patient underwent genetic testing and was diagnosed with HNPCC mutation, MLH1 suspected deleterious mutation: IVS17-2A>C.

Given the diagnosis of HNPCC mutation, the patient was referred for prophylactic hysterectomy and bilateral salpingo-oophorectomy in 2010. Surgical pathology analysis surprisingly revealed endometrioid adenocarcinoma FIGO grade 2 pT1a, Nx, Mx. Adalimumab and methotrexate were stopped

for the surgery and then discontinued after the pathology results were known. Methotrexate was resumed after 6 months for active RA. Medrol was also added for better control of rheumatoid manifestations.

Screening mammography in October 2012 was negative. In December 2013, mammography showed suspicious lesion in the outer part of the right breast with calcifications, BIRADS 4. Biopsy results showed intra-ductal carcinoma, estrogen receptor positive and progesterone receptor negative. The patient underwent right breast lumpectomy. Pathological analysis revealed solid grade 3 ductal carcinoma *in situ*.

Discussion

Lynch syndrome was first described by Dr. Henry Lynch as an aggregation of colorectal and endometrial cancers inherited in an autosomal dominant manner [1]. Germline mutations of MMR genes cause susceptibility to a hereditary form of colon cancer, hereditary nonpolyposis colon cancer (HNPCC) [2]. The diagnosis of LS can be made on the basis of family history in those families meeting the Amsterdam criteria who have tumor microsatellite instability (MSI). Alternatively, the diagnosis can be made on the basis of molecular genetic testing in an individual or family with a germline mutation in 1 of 4 mismatch repair (MMR) genes (MLH1, MSH2, MSH6, and PMS2). MLH1 and MSH2 germline mutations, which account for approximately 90% of pathogenic variants in families with LS; MSH6 pathogenic variants in about 7–10%; and PMS2 pathogenic variants in fewer than 5%. Germline deletions in EPCAM (not a mismatch repair gene) inactivate MSH2 in about 1% of individuals with Lynch syndrome [3].

Patients with Lynch syndrome are also at risk for a number of extra-colonic malignancies [4–10]. Among women, endometrial cancer is the second most common cancer associated with the LS, with an estimated lifetime risk of 40–60% [4,10]. Other associated malignancies of stomach, pancreato-biliary system, and small bowel have been described [11].

Rheumatoid arthritis is systemic autoimmune disorder in which chronic inflammation may lead to joint destruction and disability. Early recognition and aggressive management are critical to control inflammation, reduce damage, and improve outcomes. Increased risk of malignancies, especially lymphoid malignancies, have been described in patients with autoimmune diseases like RA, systemic lupus erythematosus, and Sjögren's syndrome [12,13]. Findings in a recent cohort study whose subjects included 29 patients with RA-associated lymphoma provide further indirect evidence suggesting that inflammatory activity may be a driving force in lymphoma development [14]. Epidemiological studies have demonstrated that

hematopoietic, lung, skin, and prostate cancers are increased in RA, while breast and colon cancers are decreased, with an overall slight increase in all cancers [12,15–19].

Evaluating the risk of cancer in RA patients is a 2-step process because patients are subject to increased risk of cancer due to the pathophysiology of the disease itself and some possible treatment options.

With relation to RA treatment options, effectively decreasing systemic inflammation may in fact reduce the risk for cancer, but treatment of RA using the newer biologic agents like infliximab or adalimumab has been associated with increased risk of malignancy, specifically lymphoma [16,20,21].

The rationale behind discontinuing use of biologic therapy in our patient for her RA was based upon evidence showing increased risk of malignancy with such therapy. Therefore, for treatment of rheumatoid arthritis – with thought to minimizing the risk of cancer – we would recommend traditional DMARDs such as methotrexate and leflunomide, because they are not

associated with increased risk of malignancy. However, there are no current guidelines about the use of biologic agents in the presence of active underlying malignancy [6,19]. For this reason, the therapeutic treatment of RA in the presence of LS is a challenge in which the malignancy risk factor needs to be weighed against controlling RA based on the clinical disease management as well as the patient's personal healthcare and comfort priorities.

Conclusions

We describe a patient with LS and RA presenting a therapeutic challenge because biologic agents commonly used to treat severe RA need to be used cautiously in patients with history of malignancy.

Statement

There are no financial grants or funding sources to declare. There is no conflict of interest for any authors of this manuscript.

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