

A 68-year-old man with multiple colonic polyps discovered upon routine colonoscopy

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The discovery of multiple polyps upon a routine colonoscopic screen of an apparently healthy asymptomatic elderly patient, combined with microscopic, immunohistochemical, and cytogenetic analysis, led to a diagnosis of an unusual—and often difficult to treat—malignancy.

A 68-year-old man with a history of diabetes and hypertension presented to his gastroenterologist for a routine screening colonoscopy. The patient denied having any rectal bleeding, constipation, diarrhea, or recent weight loss. At colonoscopy, multiple polyps were found throughout his colon.

Physical examination

The patient, in general, appeared to be in good health. Vital signs were stable, and there was no evidence of pallor or icterus. Examination of the patient's lymph nodes showed no palpable peripheral adenopathy. His heart rate and rhythm were regular, and both lungs were clear upon auscultation. The patient's abdomen was soft and non-tender, and there were no signs of hepatosplenomegaly. His extremities were normal.

Laboratory investigations

The patient's hemoglobin level was 10.3 g/dL. His platelet count was 183,000/ μ L and white blood cell count, 7.5×10^9 /L. Results of a chemistry panel screen were normal. Computed tomographic imaging of the patient's abdomen revealed no abnormalities. However, a colonic biopsy showed diffuse atypical lymphoid infiltration. Lymphoid cells stained positive for CD19, CD20, and CD5 and negative for CD10 and CD23.

Questions:

What is the most likely diagnosis?
What additional stain would help confirm this patient's diagnosis?

Diagnosis

A positive stain for cyclin D1 will confirm the diagnosis of mantle cell lymphoma (lymphomatous polyposis; MCL). MCL is a relatively uncommon type of non-Hodgkin's lymphoma; it accounts for approximately 5% of all lymphomas in the United States.¹ MCL is a unique clinicopathologic entity with distinct morphologic, immunophenotypic, cytogenetic, and molecular characteristics.²

Clinical features

Clinically, MCL is considered an intermediate-grade lymphoma. The median age at presentation is 58 years, with a marked male predominance. Advanced stage at presentation is typical, and bone marrow and peripheral blood involvement is commonly seen. Splenomegaly is detected in 30%–60% of MCL patients. Extranodal sites are frequently involved, including Waldeyer's ring, the liver, central nervous system, and gastrointestinal tract. A peculiar predilection for gastrointestinal involvement (up to 80% in some series) may present as a distinctive syndrome of multiple lymphomatous polyposis of the large bowel, as

illustrated by the case presented here. B symptoms are present in 30%–60% of patients. Elevated levels of lactate dehydrogenase (LDH) and β_2 -microglobulin are detected in 50% of cases.³

Histology

Four distinct histologic subtypes of MCL are recognized: mantle-zone pattern, nodular subtype, diffuse subtype, and blastoid variant. The mantle-zone variant is generally considered to have a more benign clinical course, whereas the blastoid variant is considered the most aggressive and is associated with a poorer prognosis.⁴

Immunophenotype

The immunophenotype of MCL is of a B-cell disorder expressing CD19, CD20, and CD22. A peculiar characteristic of MCL, similar to chronic lymphocytic leukemia/small cell lymphocytic lymphoma (CLL/SLL), is the almost invariable co-expression of the T cell-associated antigen CD5. Morphologically similar, MCL may be distinguished from CLL/SLL by the expression of cyclin D1 and FMC-7 and the lack of CD23 expression. CD23 is expressed in virtually all cases of CLL/SLL. Overexpression of cyclin D1 is a constant and specific finding in MCL. Another distinguishing feature of MCL that differentiates it from CLL/SLL is the moderate-to-intense surface im-

munoglobulin (Ig) staining in MCL compared with the weak surface Ig staining in CLL/SLL.

Cytogenetics

Virtually all cases of MCL carry the t(11;14)(q13;q32) translocation on karyotype analysis or fluorescence in situ hybridization (FISH). This reciprocal translocation juxtaposes the Ig heavy chain locus and the cyclin D1 gene.⁵

Management

In contrast to CLL/SLL, MCL has a relatively aggressive clinical course and responds poorly to conventional therapeutic regimens. Responses to chemotherapy such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or cyclophosphamide, vincristine, and prednisolone (CVP) are usually only partial, and even when a complete remission is achieved, the duration of remission is generally short.⁶ Autologous transplantation has not proven curative.⁷

The median survival of patients with MCL is approximately 3–4 years in most published series. The clinical parameters associated with poor prognosis include advanced age, poor performance status, advanced stage, splenomegaly, peripheral blood cell involvement, high serum LDH level, low serum albumin concentration, and anemia. Surprisingly, the International Prognostic Index is not of consistent prognostic value in MCL. The architectural pattern of nodal involvement has some predictive value: the mantle-zone pattern is associated with a higher proportion of complete remissions and longer survival, whereas the blastic variants have an aggressive course associated with a failure to obtain complete remissions and a short median survival of approximately 18 months.⁸

Researchers at The University of Texas M. D. Anderson Cancer Center have reported their experience with the

hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) regimen in a phase II trial for the treatment of MCL.⁹ This regimen is given alternately with high doses of cytarabine, methotrexate, and leucovorin rescue therapy. After 4–6 courses, consolidation therapy is begun with high-dose cyclophosphamide and total-body irradiation in patients younger than 65 years. Older patients received hyper-CVAD with no subsequent high dose of cyclophosphamide.

The 3-year overall and event-free survival rates were 92% and 72%, respectively, for previously untreated patients. The event-free survival rate of 72% is superior to the 28% event-free survival rate in an historical control group who received CHOP or a CHOP-like regimen. More recently, the same research team added rituximab (Rituxan) to the hyper-CVAD regimen, with promising early results.¹⁰ Other promising investigational approaches include radioimmunotherapy and non-myeloablative stem-cell transplantation.¹¹ Enrollment on a clinical trial is the current best therapeutic recommendation in this disease, where there is no standard approach and no clear curative strategy.

Bortezomib (Velcade), a proteasome inhibitor approved in the United States for the treatment of multiple myeloma, recently received regulatory approval for use in patients with relapsed or refractory MCL. In a phase II trial, Fisher et al¹² administered single-agent bortezomib (1.3 mg/m²) on days 1, 4, 8, and 11 of a 21-day cycle to 155 patients with relapsed/refractory MCL. The response rate in 141 evaluable patients was 33%; 8% of the patients had complete responses. The median duration of response was 9.2 months and the median time to disease progression, 6.2 months. The most common grade 3 or higher adverse events were peripheral neuropathy (13%),

fatigue (12%), and thrombocytopenia (11%).

Patient outcome

The patient presented was treated on an experimental protocol, with radioimmunotherapy and chemotherapy. At the end of treatment, a repeat colonic biopsy revealed persistent cecal involvement with MCL. The patient subsequently received pentostatin in combination with cyclophosphamide and rituximab on a clinical trial and achieved a complete remission. He remains in remission 6 months after completing all therapy.

Clinical pearls

1. The immunophenotype of MCL is of a B-cell disorder expressing CD19, CD20, and CD22. Co-expression of the T cell-associated antigen CD5 and cyclin D1 is seen almost invariably.
2. Virtually all cases of MCL carry the t(11;14)(q13;q32) reciprocal translocation on karyotype analysis or FISH.
3. In contrast to that of CLL/SLL, the clinical course of MCL is relatively aggressive and responds poorly to conventional therapeutic regimens. Responses to chemotherapy such as CHOP or CVP are usually only partial, and even when complete remission is achieved, the duration of remission is usually brief.
4. Overall and event-free survival rates of MCL patients treated with hyper-CVAD are superior to those associated historically with CHOP or CVP. The addition of rituximab to hyper-CVAD has had promising early results.
5. Bortezomib has significant activity in patients with relapsed or refractory MCL.

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