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## Constipated myeloma

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Comment on Coriu et al, page 829

## Constipated myeloma

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The molecular basis of nonsecretory myeloma in one patient is shown to be due to a crippling frameshift mutation in the kappa constant region.

**M**ost patients (~ 80%) with multiple myeloma have a monoclonal immunoglobulin (Ig) detectable in the serum, usually IgG or IgA. About 18% have only monoclonal light chains detectable in the urine (light-chain multiple myelomas [LCMMs]). Finally, about 2% do not secrete any immunoglobulin (nonsecretory multiple myelomas [NSMMs]). Recent analyses of LCMMs have shown that the tumors lack a functional IgH rearrangement, providing a molecular basis for this condition.<sup>1</sup> There has not been a comprehensive analysis of NSMMs, and previous reports have emphasized acquired mutations in the immunoglobulin light chain variable genes that lead to a block in secretion.<sup>2-4</sup> Thus from the information available there appears to be a fundamental difference in these 2 conditions, which otherwise share many features (eg, very high incidence of t(11;14)). On the one hand, LCMM lacks a functional IgH DNA rearrangement, and hence there is no RNA or protein. On the other hand, NSMM has an IgL DNA rearrangement, RNA, and protein, but suffers from crippling mutations.

In this issue, the molecular basis of nonsecretory myeloma in one patient is shown to be due to a crippling frameshift mutation in the  $\kappa$

constant region. Coriu and colleagues show that a 2-base deletion in codon 187 resulted in the loss of the normal stop codon. There was a loss of 2 cysteine molecules that are necessary for intrachain and interchain disulfide bonds. The authors postulate that the absence of C194 disrupted the 3-dimensional features of the molecule and prevented binding with the cysteine in the first heavy-chain C-domain. The misfolded  $\kappa$  chains were retained within

the plasma cell. They show that this results in an abnormal-sized protein that reacts with some but not all anti- $\kappa$  antibodies. In contrast to previously described mutations of the variable region, this represents a novel mechanism for nonsecretory myeloma. ■

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Comment on Offman et al, page 822

## Therapy-related myeloid leukemia: stochastic or idiosyncratic?

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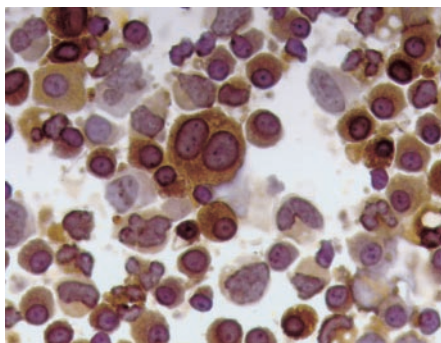
Just as life begins to return to normal, some solid organ transplant patients develop leukemia. Why?

**P**atients who have received cytotoxic therapy with chemotherapy drugs and/or radiotherapy are at risk for long-term complications from their treatment, including therapy-related myelodysplastic syndrome (tMDS) and acute myeloid leukemia (tAML). Although a causal link has not yet been proven, these neoplasms are thought to be a direct consequence of mutational events caused by cytotoxic therapy and to be independent of the primary disease. Careful clinicopathologic and cytogenetic analyses of individual cases by many investigators have defined distinctive subtypes of this disease.<sup>1</sup>

Large epidemiologic surveys have defined high-risk patient populations. Patients with Hodgkin lymphoma were the first large cohort of cancer patients who experienced prolonged survival; hundreds of cases of therapy-related leukemia have now been reported within this group. More recently, treatment has extended

the survival of patients with other cancers and they too have become at risk. In a recent report on 306 patients with therapy-related myeloid leukemia studied at the University of Chicago, 171 had lymphoma or myeloma as their primary disease, and 117 had solid tumors.<sup>2</sup> Of note, 18 had received cytotoxic therapy for nonmalignant disorders, such as autoimmune diseases, or for immunosuppression after renal allografts.

Both ionizing radiation and many, but not all, chemotherapy drugs alter cellular DNA. If not repaired, this damage is most often lethal to cells. This, of course, is the desired consequence if the target cell were a tumor cell. Occasionally, however, nonlethal and heritable mutations occur in single somatic cells. Such an alteration in DNA might involve a single base change, deletion or inactivation of a growth suppressor gene, or changes in the expression of certain critical oncogenes or



Immunocytochemical analyses of plasma cells from the patient with NSM and chemical characterization of the nonsecreted  $\kappa$  light chains. See the complete figure in the article beginning on page 829.