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## ● ● ● CLINICAL TRIALS

Comment on Mansoor et al, page 1447

# A sheep in wolf's clothing

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Most are familiar with the biblical warnings about false prophets presenting as the wolf in sheep's clothing, but in this issue of *Blood*, Mansoor and colleagues expose a sheep in wolf's clothing by shining a bright light on a newly described benign disease previously pretending to be a very bad malignancy, and doing so quite convincingly.<sup>1</sup>

**A**lthough regular practitioners of the craft of lymphoid malignancies know how to resist the siren's song and negotiate diagnostic narrows, constant alertness and up-to-date navigation maps are still required to avoid crashing onto the rocks. Nowhere are colorful tales more often told than on the steamboats crisscrossing the T/NK-cell lymphoma seas.

A young patient with papulonodular skin lesions may have a biopsy showing a deep infiltrate of large, anaplastic cells with variable proliferative rate. The tumor cells show mature T-cell markers and strong CD30 expression, but lack of ALK-1. T-cell receptor (TCR) gene analysis shows a monoclonal band. A diagnosis of CD30<sup>+</sup> anaplastic large-cell lymphoma, ALK-1 negative, is released and the patient is scheduled to begin chemotherapy. A second opinion, requested by the patient after an online search, reveals that he has type C lymphomatoid papulosis (LyP), a benign process belonging to a spectrum of CD30<sup>+</sup> lymphoproliferative disorders. The patient never gets chemotherapy. Another young patient may present with fatigue and large, tender, subcutaneous nonulcerated plaques over his upper and lower extremities. Biopsy shows a heavy, adipocyte-focused, pannicular infiltrate of CD8<sup>+</sup>, CD56<sup>-</sup>,  $\alpha$ - $\beta$  ( $\beta$ F1) T cells with a monoclonal TCR. The patient is diagnosed with subcutaneous

panniculitis-like T-cell lymphoma (SPTL) and goes on to receive aggressive chemotherapy with autologous stem cell transplant consolidation. Two years later, he is well with no evidence of progression. These stories illustrate examples of aggressive mimicry by lymphoproliferative disorders—LyP<sup>2</sup> and  $\alpha$ / $\beta$  SPTL,<sup>3</sup> respectively—that can imitate very aggressive subtypes of peripheral T-cell lymphoma (PTCL), sending shockwaves through the oncology ranks and prompting aggressive chemotherapy, almost always unnecessarily.

Although exclusive cutaneous involvement should immediately alert one to the possibility of a pretender lesion, or at least a more indolent subtype of lymphoma, Mansoor et al demonstrate that T/NK-cell lymphoma mimics are not restricted to the skin. They describe 8 patients (mostly white women without prior history of gastrointestinal pathology) who presented with vague abdominal symptoms and had endoscopic evidence of mucosal lesions largely restricted to the colon (6 of 8), with additional sites of involvement in 4 (gastric and/or duodenal). Biopsies revealed dense mucosal infiltrates of intermediate to large NK cells (CD56<sup>+</sup>, TIA-1<sup>+</sup>, Granzyme B<sup>+</sup>, cCD3<sup>+</sup>), without detectable EBV (EBV-encoded RNA [EBER]) and with polyclonal TCR rearrangements. Sheets of atypical cells

were seen in some cases, with destruction of mucosal glands, raising the concern for lymphoma. However, no angiodestruction was observed. After extensive imaging, none of the patients had lymphadenopathy or organomegaly. Peripheral blood and bone marrow (6/8) did not show expansions of NK cells or large granular lymphocytes.

The original pathologic diagnoses, before the authors' review, are not explicitly reported, but in at least 3 patients a diagnosis of NK-cell lymphoma was evidently made, leading to the initiation of chemotherapy, followed in 2 patients by consolidation with autologous stem cell transplantation. This is not surprising, considering that oncologists (and transplant hematologists) are constantly reminded of how bad extranodal NK-cell lymphomas are. What is more remarkable is the fact that 5 patients did not start chemotherapy and were instead observed, for a very long time (median 30 months, range 22-120), without developing signs of progression or transformation. It would be interesting to know how the original diagnosis was phrased and how it guided the clinician's choice, which was in retrospect a very wise one (ie, who failed to blink, the pathologist, the oncologist, or both?). There is a moral somewhere in that story.

After a very careful characterization and with the benefit of an extremely long follow-up, Mansoor et al conclude that these lesions are consistent and homogenous enough to be proposed as a new entity that they call "NK-cell enteropathy." This entity, if confirmed, should be added to the list of known pretenders, and should become known far and wide across the land, lest aggressive chemotherapy be unleashed upon it. Although much remains to be offered in the way of guidance, clinicians facing a biopsy report of an atypical CD56<sup>+</sup> NK-cell infiltrate should first pay attention to the EBV status of the lesion. Strong EBV positivity (EBER) should indeed send chills down one's spine, as the odds of an extranodal NK-cell lymphoma, nasal type, rather than the entity described by Mansoor et al, is much higher. The proliferation fraction may also help, but the number of MIB-1/Ki67-positive cells can vary significantly across the biopsy, making it a less reliable discriminator between benign and malignant lesions.

In their discussion, Mansoor et al comprehensively and helpfully review the differential diagnosis of this new entity and offer some

thoughts on its possible etiology. A reactive process associated with a predominant NK-cell response across the gastrointestinal tract seems to be ongoing in these patients, as evidenced by the long persistence of the lesions on follow-up. It would be interesting to study the level of expression of cytokines such as IL-15 and IL-1, which are abundant in the mucosa-associated lymphoid tissue (MALT), especially in patients with celiac disease<sup>4</sup> and other inflammatory bowel disorders,<sup>5</sup> and have been shown to stimulate growth of immature NK cells found in MALT.<sup>6</sup>

As a final commentary, considering that the single most common anatomical site of involvement in Mansoor's cases is the colon, one might consider the diagnostic term "NK-cell colitis" (atypical or not) as possibly more fitting than "enteropathy." In that regard, despite the lack of symptoms and a presumption of normal immunity, one wonders whether stains for cytomegalovirus or other human herpesviruses should have been performed in these lesions, to exclude infections known to be recognized by NK cells. And, was there a family history of autoimmune diseases, immunodeficiency, or hematologic malignancies? Future reports of this fascinating new disease entity may have to address these issues. Nonetheless, we

commend the authors for what George Orwell famously observed: "To see what is in front of one's nose needs a constant struggle."

*Conflict-of-interest disclosure:* The authors declare no competing financial interests. ■

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## CLL: a supplementary question?

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In this issue of *Blood*, Shanafelt and colleagues provide the first evidence that vitamin D deficiency is a risk factor for disease progression in chronic lymphocytic leukemia (CLL).<sup>1</sup> Their findings imply that dietary vitamin D supplementation could potentially modify the natural history of this incurable disease.

It has been estimated that approximately 1 billion people worldwide have vitamin D insufficiency due to reduced exposure to sunlight or inadequate dietary intake.<sup>2</sup> Vitamin D plays a central role in maintaining serum calcium and skeletal homeostasis but is also involved in the regulation of other vital cellular processes including differentiation, proliferation, apoptosis, and angiogenesis.<sup>3</sup> Although its precise mechanisms of action remain incompletely resolved, vitamin D predominantly exerts its effects through the binding of calcitriol, the active form of vitamin D, to its

cognate nuclear vitamin D receptor (VDR). A heterodimer, formed with the retinoid X receptor (RXR), then acts as a transcription factor by binding to specific genomic sequences (vitamin D response elements) resulting in altered gene transcription.<sup>4</sup> The classic target organs of vitamin D are the intestines, kidney, and bone, but several other tissues also express VDRs including normal and neoplastic hematopoietic cells.<sup>5,6</sup>

A large number of studies have investigated a possible role for vitamin D in cancer prevention but, until now, none have shown

that this secosteroid hormone is important in CLL. The study of Shanafelt et al<sup>1</sup> clearly demonstrates that vitamin D insufficiency is an independent risk factor in this disease. Remarkably, its prognostic power was evident even in early-stage patients (Rai stage 0) and retained independent prognostic significance in the presence of most of the major known risk factors in multivariate analysis. From a clinical perspective, vitamin D insufficiency represents the first potentially modifiable prognostic marker in CLL by presenting the opportunity for patients to have their serum vitamin D levels checked and, if they are deficient, vitamin D supplements administered to correct the deficit. Given that appropriate vitamin D supplements are likely to have a minimal side-effect profile, it seems plausible that they could be safely incorporated into the "watch-and-wait" strategy currently used for early-stage disease patients. If nothing else, this may well have positive psychological effects for many patients who struggle with feelings of powerlessness after being told they have leukemia that may progress.

Although we still await formal proof that normalizing vitamin D levels can improve clinical outcomes in this disease, there are certainly grounds for optimism. Previous gene expression profiling and protein analysis identified that the VDR is highly expressed in CLL cells compared with normal B and T lymphocytes.<sup>7,8</sup> Furthermore, pharmacologic doses of a vitamin D analog caused preferential *in vitro* cell killing in primary CLL cells through a p53-independent mechanism.<sup>8</sup> Taken together, the evidence points toward a potentially important role for vitamin D not only as a prognostic marker but also as a therapeutic target in CLL. On a cautionary note, it would appear that vitamin D levels are subject to heritable genetic variation with 3 pivotal polymorphisms recently being identified.<sup>9</sup> Furthermore, VDR polymorphisms have been associated with the risk of developing cancer and cancer progression although there are no reported studies in CLL.<sup>10</sup> Therefore, it may not be possible to correct vitamin D insufficiency with dietary supplementation in at least some CLL patients. Only a prospective, well-designed, randomized, control clinical trial of vitamin D supplementation will prove whether we have truly "crossed the Rubicon" in CLL and identified a way of modifying the clinical course of this incurable disease with a simple vitamin tablet.