Hypertrophic Pulmonary Osteoarthropathy and Tripe Palms

Hayder Saeed, M.D., and Suleiman Massarweh, M.D.

A 56-year-old female smoker presented with cough, a weight loss of 27 kg over a period of 6 months, and diffuse bone pain. The palms had a raised velvety texture (Panel A), and there was digital clubbing (inset). There was also a nodule (1 cm in diameter) in the left breast. A computed tomographic (CT) scan of the chest showed a mass (11 cm in diameter) in the upper lobe of the right lung (Panel B). A bone scan (Panel C) showed areas of uptake of technetium-99m-labeled methylene diphosphonate that were consistent with metastases (arrowhead), as well as diffuse bone pain. The palms presented with hypertrophic pulmonary osteoarthropathy and tripe palms (acanthosis nigricans), as well as diffuse linear uptake in the femoral and tibial bones, consistent with hypertrophic pulmonary osteoarthropathy (arrows). Examination of specimens obtained by CT-guided biopsy of the lung mass and fine-needle aspiration of the breast nodule were consistent with large-cell adenocarcinoma. Hypertrophic pulmonary osteoarthropathy and tripe palms (acanthosis palmaris) are paraneoplastic manifestations of, most frequently, lung and gastric carcinomas. The patient was discharged with plans to start outpatient chemotherapy. She received one cycle of pemetrexed and carboplatin, but her performance status declined. Because of worsening bone pain, she received palliative radiation to the lower spine and right lower tibial mass.
Low-Dose Interleukin-2 in HCV-Induced Vasculitis

David Saadoun, M.D., Ph.D., and others

**BACKGROUND**

Patients with vasculitis induced by the hepatitis C virus (HCV) have reduced levels of regulatory T cells (Tregs). Resolution of HCV infection correlates with cure of vasculitis and the recovery of Treg levels. We reasoned that interleukin-2, a cytokine that promotes Treg survival and function, could be beneficial for patients with vasculitis that is resistant to HCV therapy.

**METHODS**

We investigated the safety and immunologic effects of the administration of low-dose interleukin-2 in a prospective open-label, phase 1/phase 2a study. Ten patients with HCV-induced vasculitis that was refractory to conventional antiviral therapy, rituximab therapy, or both and who were not receiving glucocorticoid or immunosuppressant therapy, received one course of interleukin-2 (1.5 million IU per day) for 5 days, followed by three 5-day courses of 3 million IU per day at weeks 3, 6, and 9. Both the safety of the treatment and its effectiveness were evaluated, the latter by monitoring the Treg response and the clinical signs of HCV vasculitis.

**RESULTS**

No adverse events reached a level higher than grade 1. The treatment did not induce effecter T-cell activation, vasculitis flare, or increased HCV viremia. We observed a reduction in cryoglobulinemia in 9 of 10 patients and improvement of vasculitis in 8 of 10. Administration of low-dose interleukin-2 was followed by an increase in the percentage of CD4+, CD25high, forkhead box P3 (FOXP3+) Tregs (Emax (maximum value) ÷ baseline value × 100 = 420%) with potent continued on next page

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**RESULTS IN ARTHRITIS/RHEUMATOLOGY**

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monocytes and macrophages, and T cells, natural killer cells, B cells, interleukin-2. A major shift in the therapeutic use of therapy. These results signal a major shift in the therapeutic use of interleukin-2.

Interleukin-2 activates multiple immune-cell subsets, including T cells, natural killer cells, B cells, monocytes and macrophages, and neutrophils. Interleukin-2 alone has activity in a small fraction of patients with metastatic melanoma and has been used to support in vitro expansion of effector cells in patients with cancer and infection with the human immunodeficiency virus (HIV). Interleukin-2 remains the only curative treatment for patients with metastatic renal-cell carcinoma. However, the use of interleukin-2 has been limited because of its toxicity at high doses and limited efficacy. Recent studies have shown that the primary function of interleukin-2 is the generation and survival of an essential regulatory population of lymphocytes, regulatory T (Treg) cells, which function to inhibit immune responses and prevent autoimmune disease.

Treg cells, a small subset of CD4+ T cells identified by their constitutive expression of CD25 (the alpha chain of the interleukin-2 receptor) and the lineage-specific transcription factor FOXP3, control immune responses in multiple conditions, including infectious diseases, asthma, and autoimmunity. Interleukin-2 is essential for the development, survival, and function of Treg cells. Thus, the functions of interleukin-2 during a T-cell response appear to be

**EDITORIAL**

The Yin and Yang of Interleukin-2–Mediated Immunotherapy

Jeffrey A. Bluestone, Ph.D.

In this [December 1] issue of the journal [N Engl J Med 2011;365], the findings of two case series suggest that in vivo treatment with interleukin-2 can suppress immune-mediated diseases. In one study, Koreth et al. found that low-dose interleukin-2 was associated with reversal of glucocorticoid-refractory chronic graft-versus-host disease (GVHD) in patients who had undergone allogeneic hematopoietic stem-cell transplantation (HSCT) for the treatment of lymphomas and leukemias. The control of chronic GVHD was not accompanied by the relapse of cancer in any patient. In a second small case series, Saadoun et al. found that treatment of patients with hepatitis C virus (HCV)–related vasculitis with low-dose interleukin-2 led to substantial clinical improvement in both cryoglobulinemia and vasculitis — clinical manifestations that in these patients had been refractory to antiviral and anti-B-cell therapy. These results signal a major shift in the therapeutic use of interleukin-2.

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**CONCLUSIONS**

The trial showed that low-dose interleukin-2 was not associated with adverse effects and led to Treg recovery and concomitant clinical improvement in patients with HCV-induced vasculitis, an autoimmune condition. (Funded by the French Agency for Research on AIDS and Viral Hepatitis [ANRS] and others; ClinicalTrials.gov number, NCT00574652.)
Tophaceous Gout

Nikolaos Samaras, M.D., and Cecile Rossi, M.D.

A 74-year-old woman with chronic renal failure was admitted for diarrhea and functional impairment. She was noted to have a tender, soft swelling of the medial and distal phalanx of the right index finger (Panel A). She had no history of joint inflammation or any recent use of diuretics but reported consuming a bottle of wine daily. Plain radiography showed substantial osteolysis of the distal phalanx and partial osteolysis of the medial phalanx (Panel B). Needle aspiration yielded a white viscous liquid, with numerous urate crystals identified on polarized light microscopy (Panel C). Abdominal computed tomography did not identify any uric acid stones. Slightly elevated levels of serum uric acid (386 μmol per liter) were attributed to chronic renal failure and untreated hypothyroidism. Bone destruction was attributed to tophaceous gout. Treatment with allopurinol and colchicine was initiated, and the patient was referred to an orthopedist who performed an arthrodesis of the remainder of the medial and distal phalanges. The patient was discharged without further complications.

Bluestone — from page 3

antagonistic. Many human diseases are characterized by an imbalance of effector T (Teff) cells and Treg cells (see figure). A reduced frequency or function of Treg cells, or both, characterizes autoimmune diseases, including HCV-related vasculitis and chronic GVHD. Conversely, although Treg cells may prevent tissue damage caused by unregulated pathogen-specific Teff responses and inflammation, high levels of Treg cells may prevent efficient clearance of infectious agents and hamper antitumor responses. Strategies for cell therapy aimed at restoring the Teff:Treg balance are being studied.

The expansion of numbers of Treg cells in chronic GVHD, described by Koreth et al., and in HCV-related autoimmune vasculitis, described by Saadoun et al., builds on the use of interleukin-2 to promote the expansion of Treg cells in animal models of GVHD, autoimmunity, and even some studies involving patients with HIV infection. Interleukin-2 treatment greatly increases the Teff:Treg ratio, although the results are often transient and limited to the treatment window. The dose of interleukin-2 matters. Low-dose interleukin-2 therapy potentially induces Treg expansion, whereas high-dose interleukin-2 treatment results in a relative increase in the Teff population (see figure). Koreth et al. treated 28 patients with chronic GVHD with low-dose interleukin-2 subcutaneously. Even without a control group, the treatment appeared extremely effective, with no relapse of cancer or progression of chronic GVHD.

Of the 23 patients who could be evaluated, 11 had stable disease and 12 had an objective partial response. Importantly, Treg-cell counts, but not conventional T-cell (Tcon) counts, significantly increased during treatment, resulting in an increase in the Treg:Tcon ratio that was more than five times as high as the baseline level. No significant change in CD8+ T-cell counts was noted, perhaps because of the use of sirolimus and other immunosuppressive agents.

The beneficial effect of interleukin-2 treatment in the study by Koreth et al. may not be solely due to increased Treg cells, since Treg-cell counts increased in all patients but were not statistically different between patients who had a response and those who did not have a response. A recent clinical trial of Treg-cell infusion to prevent acute GVHD showed improved GVHD but no statistical difference with respect to relapse of cancer. Moreover, as shown in Table 1 of the article by Koreth et al., individual patients had been receiving quite distinct immunosuppressive agents (glucocorticoids, mycophenolate mofetil, calcineurin inhibitors, and sirolimus). The investigators did not discuss whether these distinct clinical responses correlated with various different adjunct immunosuppressive therapies. In the study by Saadoun et al., the use of low-dose interleukin-2 in HCV-related autoimmune vasculitis was similarly effective and minimally toxic.

There was a significant reduction in cryoglobulinemia in 9 of 10 patients and an improvement in vasculitis in 8 of 10, which correlated with a reduced inflammatory gene signature.

However, the effects of interleukin-2 may be complex. Natural killer cells may also be contributing to the efficacy. Interleukin-2 therapy increased the number of natural killer cells; such cells may kill activated Teff cells. Interestingly, in a clinical trial of interleukin-2 and sirolimus in autoimmune diabetes (Proleukin and Rapamune in Type 1 Diabetes, ClinicalTrials.gov number, NCT00225809), natural killer-cell counts increased and may have been responsible for a transient decrease in the function of islet beta cells. Unfortunately, both studies had only a limited analysis of other subsets of peripheral-blood mononuclear cells, including eosinophils; eosinophils have been shown to increase dramatically in other studies of interleukin-2 therapy.

Overall, low-dose interleukin-2 appeared to be safe; serious complications or infections occurred in few patients. The concern that suppressing T-cell immunity by up-regulating Treg cells would put the patient with HCV at risk for a worsened viral load appears groundless in this small series. However, the possible long-term effects of interleukin-2 treatment are uncertain, since these patients were followed for only 3 to 4 months. A sustained increase in Treg cells may be problematic in patients with ongoing acute or chronic infections. Marine studies have shown that Treg cells can prevent GVHD while preserving graft-versus-leukemia activity. However, the adverse effect of Treg...
Evidence-Based Medicine in the EMR Era

Jennifer Frankovich, M.D., and others

Many physicians take great pride in the practice of evidence-based medicine. Modern medical education emphasizes the value of the randomized, controlled trial, and we learn early on not to rely on anecdotal evidence. But the application of such superior evidence, however admirable the ambition, can be constrained by trials’ strict inclusion and exclusion criteria—or the complete absence of a relevant trial. For those of us practicing pediatric medicine, this reality is all too familiar. In such situations, we are used to relying on evidence at Levels III through V—expert opinion—or resorting to anecdotal evidence. What should we do, though, when there aren’t even meager data available and we don’t have a single anecdote on which to draw?

We recently found ourselves in such a situation as we admitted to our service a 13-year-old girl with systemic lupus erythematosus (SLE). Our patient’s presentation was complicated by nephrotic-range proteinuria, antiphospholipid antibodies, and pancreatitis. Although anticoagulation is not standard practice for children with SLE even when they’re critically ill, these additional factors put our patient at potential risk for thrombosis, and we considered anticoagulation. However, we were unable to find studies pertaining to anticoagulation in our patient’s situation and were therefore reluctant to pursue that course, given the risk of bleeding. A survey of our pediatric rheumatology colleagues—a review of our collective Level V evidence, so to speak—was equally fruitless and failed to produce a consensus.

Without clear evidence to guide us and needing to make a decision swiftly, we turned to a new approach, using the data captured in our institution’s electronic medical record (EMR) and an innovative research database. The platform, called the Stanford Translational Research Integrated Database Environment (STRIDE), acquires and stores all patient data contained in the EMR, at our hospital and provides immediate advanced text searching capability. Through STRIDE, we could rapidly review data on an SLE cohort that included pediatric patients with SLE cared for by clinicians in our division between October 2004 and July 2009. This “electronic cohort” was originally created for use in studying complications associated with pediatric SLE and exists under a protocol approved by our institutional review board.

Of the 98 patients in our pediatric lupus cohort, 10 patients developed thrombosis, documented in the EMR, while they were acutely ill. The prevalence was higher among patients who had persistent nephrotic-range proteinuria and pancreatitis (see table). As compared with our patients with lupus who did not have these risk factors, the risk of thrombosis was 4.7 (95% confidence interval [CI], 3.3 to 9.6) among patients with persistent nephrosis and 11.8 (95% CI, 3.8 to 27) among those with pancreatitis. This automated cohort review was conducted in less than 4 hours by a single clinician. On the basis of this real-time, informatics-enabled data analysis, we made the decision to give our patient anticoagulants within 24 hours after admission. Our case is but one example of a situation in which the existing literature is insufficient to guide the clinical care of a patient. But it illustrates a novel process that is likely to become much more standard with the widespread adoption of EMRs and more sophisticated informatics tools. Although many other groups have highlighted the secondary use of EMR data for clinical research,3,5 we have now seen how the same approach can be used to guide real-time clinical decisions. The rapid electronic chart review and analysis were not only feasible, but also more helpful and accurate than physician recollection and pooled colleague opinion. Such real-time availability of data to guide decision making has already transformed other industries,6 and the growing prevalence of EMRs along with the development of sophisticated tools for real-time analysis of deidentified data sets will no doubt advance the use of this data-driven approach to health care delivery. We look forward to a future in which health information systems help physicians learn from every patient at every visit and close the feedback loop for clinical decision making in real time.

Did we make the correct decision for our patient? Thrombosis did not develop, and the patient did not have any sequelae related to her anticoagulation; truthfully, though, we may never really know. We will, however, know that we made the decision on the basis of the best data available—acting, as the fictional detective Nero Wolfe would say, “in the light of experience as guided by intelligence.”7 In the practice of medicine, one can’t do better than that.

Results of Electronic Search of Patient Medical Records (for a Cohort of 98 Pediatric Patients with Lupus) Focused on Risk Factors for Thrombosis Relevant to Our 13-Year-Old Patient with Systemic Lupus Erythematosus

<table>
<thead>
<tr>
<th>Thrombosis risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence of Thrombosis</td>
</tr>
<tr>
<td>Relative Risk (95% CI)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome or Risk Factor</th>
<th>Keywords Used to Conduct Expeditious Electronic Search</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombosis resulting from anticoagulation: “Thrombosis,” “Thrombosis,” “Blood clot”</td>
<td>10/94 (10) Not applicable</td>
</tr>
<tr>
<td>Heavy proteinuria (&gt;2.5 g per deciliter)</td>
<td>“Nephrosis,” “Nephrotic,” “Proteinuria” 8/16 (22) 7.8 (1.7–50)</td>
</tr>
<tr>
<td>Present &gt;60 days</td>
<td>“Urine protein” 7/23 (30) 14.7 (3.3–96)</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>“Pancreatitis,” “Lipase” 5/8 (63) 11.8 (3.8–27)</td>
</tr>
<tr>
<td>Antiphospholipid antibodies</td>
<td>“Aspirin” 6/51 (12) 1.0 (0.3–3.7)</td>
</tr>
</tbody>
</table>

4 In all cases, the sentences surrounding the keywords were manually reviewed to determine their relevance to our patient. Pancreatitis was defined as an elevated “lipase” level (twice the upper limit of normal) consisting with abdominal pain. We used the word “aspirin” as a proxy for antiphospholipid antibodies, since it is standard practice at our institution to give all patients with these antibodies aspirin; if “aspirin” was found in the chart, than antiphospholipid-antibody status was confirmed by investigating the laboratory results.

From the Division of Rheumatology (J.F.), the Division of Systems Medicine (C.A.L.), and the Division of Nephrology (S.M.J.), Department of Pediatrics, Stanford University School of Medicine, Palo Alto, CA. Full content, including all tables and figures, can be found at www.nejm.org/doi/full/10.1056/NEJMp1108726.

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From the University of California, San Francisco, San Francisco. Full content, including all tables and figures, can be found at www.nejm.org/doi/full/10.1056/NEJMp1109090.
Cold Urticaria, Immunodeficiency, and Autoimmunity Related to PLCG2 Deletions

Michael J. Ombrello, M.D., and others

BACKGROUND
Mendelian analysis of disorders of immune regulation can provide insight into molecular pathways associated with host defense and immune tolerance.

METHODS
We identified three families with a dominantly inherited complex of cold-induced urticaria, antibody deficiency, and susceptibility to infection and autoimmunity. Immunophenotyping methods included flow cytometry, analysis of serum immunoglobulins and autoantibodies, lymphocyte stimulation, and enzymatic assays. Genetic studies included linkage analysis, targeted Sanger sequencing, and next-generation whole-genome sequencing.

RESULTS
Cold urticaria occurred in all affected subjects. Other, variable manifestations included atopy, granulomatous rash, autoimmune thyroiditis, the presence of antinuclear antibodies, sinopulmonary infections, and common variable immunodeficiency. Levels of serum IgM and IgA and circulating natural killer cells and class-switched memory B cells were reduced. Linkage analysis showed a 7-Mb candidate interval on chromosome 18q in one family, overlapping by 3.5 Mb a disease-associated haplotype in a smaller family. This interval includes PLCG2, encoding phospholipase Cγ2 (PLCG2), a signaling molecule expressed in B cells, natural killer cells, and mast cells. Sequencing of complementary DNA revealed heterozygous transcripts lacking exons 20 through 22 in two families and a third family. Genomic sequencing identified three distinct in-frame deletions that cosegregated with disease. These deletions, located within a region encoding an autoinhibitory domain, result in protein products with constitutive phospholipase activity. PLCG2-expressing cells had diminished cellular signaling at 37°C but enhanced signaling at subphysiologic temperatures.

CONCLUSIONS
Genomic deletions in PLCG2 cause gain of PLCγ2 function, leading to signaling abnormalities in multiple leukocyte subsets and a phenotype encompassing both excessive and deficient immune function. (Funded by the National Institutes of Health Intramural Research Programs and others.)
ORIGINAL ARTICLE

Bone-Density Testing Interval and Transition to Osteoporosis in Older Women

Margaret L. Gourlay, M.D., and others

BACKGROUND

Although bone mineral density (BMD) testing to screen for osteoporosis (BMD T score, −2.50 or lower) is recommended for women 65 years of age or older, there are few data to guide decisions about the interval between BMD tests.

METHODS

We studied 4957 women, 67 years of age or older, with normal BMD (T score at the femoral neck and total hip, −1.00 or higher) or osteopenia (T score, −1.01 to −2.49) and with no history of hip or clinical vertebral fracture or of treatment for osteoporosis, followed prospectively for up to 15 years. The BMD testing interval was defined as the estimated time for 10% of women to make the transition to osteoporosis before having a hip or clinical vertebral fracture, with adjustment for estrogen use and clinical risk factors. Transitions from normal BMD and from three subgroups of osteopenia (mild, moderate, and advanced) were analyzed with the use of parametric cumulative incidence models. Incident hip and clinical vertebral fractures and initiation of treatment with bisphosphonates, calcitonin, or raloxifene were treated as competing risks.

RESULTS

The estimated BMD testing interval was 16.8 years (95% confidence interval [CI], 11.5 to 24.6) for women with normal BMD, 17.3 years (95% CI, 13.9 to 21.5) for women with mild osteopenia, 4.7 years (95% CI, 4.2 to 5.2) for women with moderate osteopenia, and 1.1 years (95% CI, 1.0 to 1.3) for women with advanced osteopenia.

CONCLUSIONS

Our data indicate that osteoporosis would develop in less than 10% of older, postmenopausal women during rescreening intervals of approximately 15 years for women with normal bone density or mild osteopenia, 5 years for women with moderate osteopenia, and 1 year for women with advanced osteopenia. (Funded by the National Institutes of Health.)

Unadjusted Cumulative Incidence of Osteoporosis According to Baseline T-Score Range.

The proportion of women who had a transition to osteoporosis is shown as a function of time. The cumulative incidence curves were estimated by means of parametric cumulative incidence models for interval-censored data. The dashed horizontal line marks the 10% threshold for the transition to osteoporosis; where this line intersects each cumulative incidence curve, a vertical dashed line to the x axis marks the estimated testing interval. The analysis of women with osteopenia at baseline is based on three T-score groups and included the 513 women who made the transition from normal BMD to osteopenia and had at least one subsequent examination with BMD recorded.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Case 1-2012: An 82-Year-Old Man with Persistent Ulcers on the Hands

Daniela Kroshinsky, M.D., and others

SUMMARY

- An 82-year-old man was admitted to this hospital because of a 4-month history of bullous and ulcerated skin lesions on the hands, which did not respond to antibiotic therapy and debridement.
- A diagnostic procedure was performed.

FINAL DIAGNOSIS

- Pyoderma gangrenosum due to a myelodysplastic syndrome (refractory cytopenia with multilineage dysplasia).

From the Departments of Dermatology (D.K.) and Pathology (M.P.H., R.P.H.), Massachusetts General Hospital; and the Departments of Dermatology (D.K.) and Pathology (M.P.H., R.P.H.), Harvard Medical School — both in Boston. Full content, including all tables and figures, can be found at www.nejm.org/doi/full/10.1056/NEJMcpc1104568.
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- Reduces swollen and painful joint counts and maintains these improvements at 5 years3
- Early treatment in combination with methotrexate helps achieve remission - structurally, functionally and clinically1
- Safety profile established over 10 years of continuous therapy in clinical trials2
- Registry results showed lowest incidence of Tuberculosis4,8
- No dose escalation required for most patients10

*Registry results versus adalimumab and infliximab

[References]

[Endnotes]