mechanisms. Macrophages express TF in a cryptic form on the cell surface, but cellular stress signals, such as ATP triggering the purinergic P2X7 receptor, can rapidly activate TF by increasing extracellular PS coupled to inflammasome/caspase 1–dependent release of highly procoagulant extracellular vesicles.[5] TF can also be activated by an inflammasome-caspase 11–dependent pathway leading to gasdermin D–dependent PS exposure and pyroptoptosis.[6] HMGB1 activates this noncanonical inflammasome pathway by delivering LPS for cytosolic activation of caspase 11, gasdermin D, and the PS scramblase transmembrane protein 16F. As shown in this paper, the resulting externalization of PS was required for macrophage TF procoagulant activity and, accordingly, inhibition of PS reduces DIC in sepsis challenged mice.

DIC is typically viewed as a failure of critical anticoagulant mechanisms due to reciprocal amplification of inflammation and coagulation. The current study provides conceptually new insight that a specific arm of the innate immune response connects tissue stress to the posttranslational activation of TF on immune cells. Complement factor (C) 3, which is part of the other major plasmatic innate defense pathway, is also linked to TF activation and participates in thrombosis and autoimmune signaling by supporting thiol isomerase–dependent conformational changes in TF.[3,4] Blockade of C3 prevents the coagulopathy in sepsis,[7] and HMGB1 can activate C3 in sterile inflammation.[8] It is therefore conceivable that the identified role of extracellular HMGB1 in creating a procoagulant environment on the cell surface extends to complement-mediated effects that allosterically activate TF.

Not only are TRIF-IFN-α/βR1 signaling and coagulation connected in this link promoting DIC, but also, intriguingly, the TF coagulation initiation signaling complex activating protease activated receptor 2 directly controls TIr4-TRIF responses in sepsis.[9] These signaling events are further regulated in innate immune cells by the sepsis-protective anticoagulant pathway.[10] The new connection of DIC induction uncovered here may, therefore, prove to be part of a broader crosstalk between coagulation and immunity in infectious diseases.

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CLINICAL TRIALS AND OBSERVATIONS

Comment on Mahévas et al, page 1101

Of lions, shar-pei, and doughnuts: a tale retold

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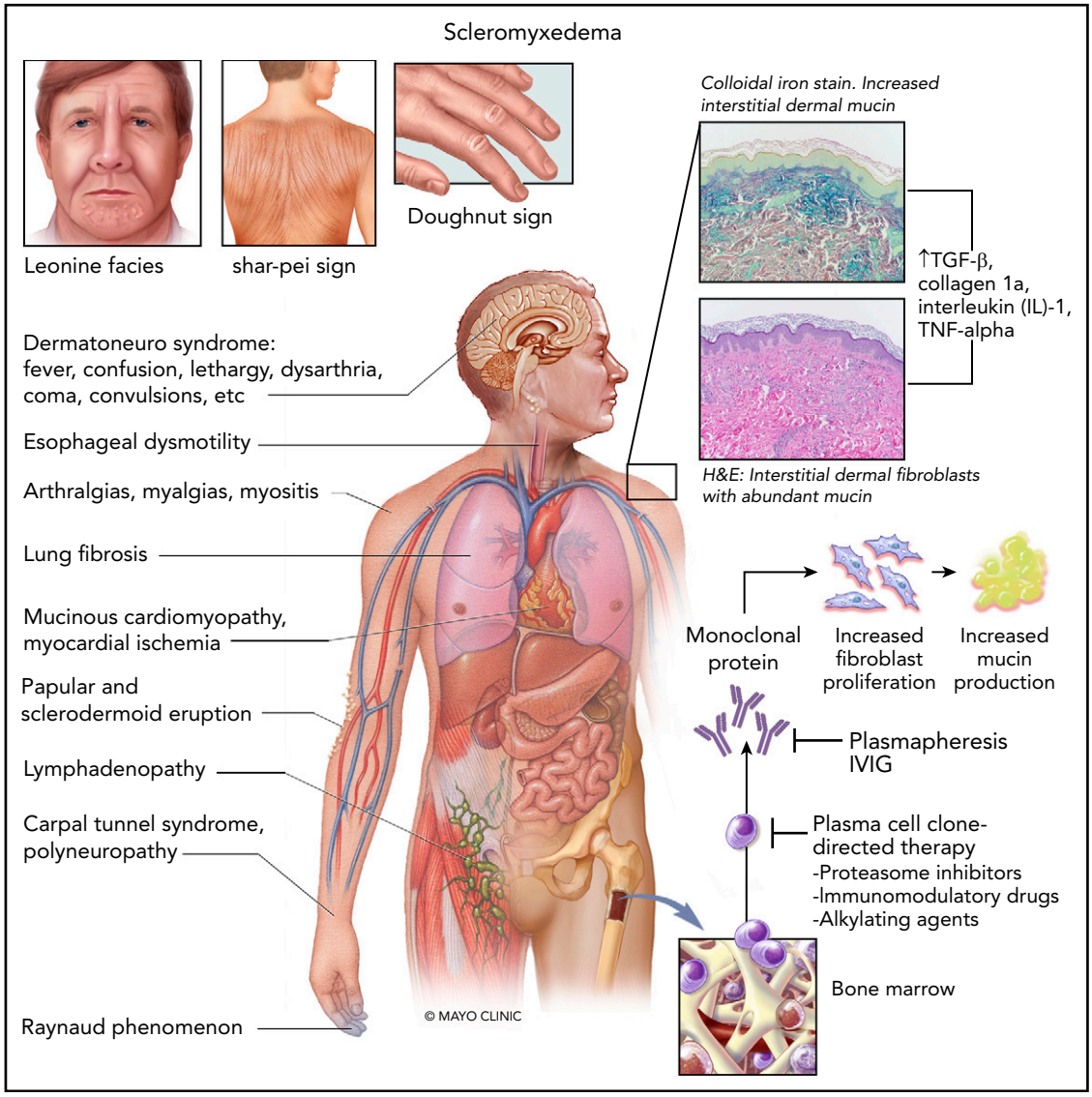
In this issue of *Blood*, Mahévas et al demonstrate that an immunomodulatory drug or a proteasome inhibitor partnered with dexamethasone can lead to a clinically meaningful improvement in severe cases of scleromyxedema that are refractory to high-dose IV immunoglobulin (IVIG).[1]

Scleromyxedema is a fibrosing dermopathy, more easily explicable to a hematologist with its recent placement under the umbrella of monoclonal gammopathy of clinical significance, or more specifically, monoclonal gammopathy of cutaneous significance.[2,3] Timely recognition of this multisystem, progressive disease continues to elude clinicians despite its characteristic cutaneous phenotype (see figure). It is diagnosed on the basis of the following well-established criteria: (1) papular cutaneous eruption in a scleroderma-like distribution; (2) microscopic triad of dermal mucin deposition, fibroblast proliferation, and fibrosis; (3) the presence of monoclonal gammopathy; and (4) the absence of thyroid dysfunction indicative of myexedema.[4] Not infrequently, potentially lethal complications related to extracutaneous involvement, including the central nervous system (dermato-neuro syndrome), respiratory system, and/or heart (mucinous cardiomyopathy or myocardial ischemia), are encountered.[3]

Several gaps in our knowledge of scleromyxedema, a disease with an unpredictable clinical course, persist. In addition, a large void in the mechanistic studies designed to characterize the disease biology leading to rational therapy exists. Notwithstanding the sparse and contradictory data attempting to implicate the circulating monoclonal protein in the pathophysiology of scleromyxedema, and to precisely define its potential relationship with fibroblast proliferation and mucinosis,[4-6] the responses observed with plasma cell–targeting therapies, including high-dose melphalan followed by stem-cell rescue, have been clearly documented.[4,7] The lack



Clonal plasma cells residing within the bone marrow produce circulating monoclonal proteins that may subsequently lead to increased proliferation of dermal fibroblasts and excess mucin production. This pathologic process results in the myriad of depicted cutaneous and extracutaneous manifestations of scleromyxedema. Key cutaneous signs depicted include (a) leonine facies: deeply furrowed "lumpy" face with prominent superciliary arches resembling that of a lion, (b) the shar-pei sign: deep furrows in the skin of the back characteristic of the shar-pei breed of dog, and (c) the doughnut sign: induration of skin with central depression over proximal interphalangeal joint. Possible therapies include treatments directed against the plasma cell clone or the circulating monoclonal protein. H&E, hematoxylin and eosin; TGF-β, transforming growth factor-β; TNF-alpha, tumor necrosis factor-alpha. Joanna R. King (Mayo Clinic, Rochester) provided assistance to the authors in creating the figure; Julia S. Lehman (Mayo Clinic, Rochester) shared inlay histology images for the figure.

of randomized controlled trials, however, forces the clinicians to relegate their clinical decision making to a lower level of evidence extracted from case reports and series.

In yet another relatively large (n = 33), multi-institutional, retrospective French series, with a respectable follow-up (median 4.3 years; range 0.5 to 13 years), Mahévas et al reinforce the findings of prior studies demonstrating substantial efficacy, particularly in nonsevere cases, of the commonly used IVIG therapy, presumably due to its immunomodulatory actions, including the anticytokine effect, neutralization of the circulating autoantibodies by anti-idiotype antibodies, and the blockade of Fc receptors on macrophages.[4] However, this and other studies have demonstrated high rates of disease relapse upon discontinuation of IVIG or abbreviation of the maintenance phase of treatment. Importantly, in the small subset of severe and/or IVIG refractory cases (n = 7) of the current study, remarkable activ-ity of plasma cell clone-directed therapies, lenalidomide and bortezomib, was noted as suggested by the attainment of both hematologic and clinical responses in the majority of patients. However, the clinical responses did not necessarily correlate with the hematologic responses. Incorporation of such novel agents that are amenable to long-term administration by virtue of their favorable toxicity profile likely contributed to the improved patient outcomes in this study as exemplified by the indirect comparison with other series: mortality rate, 38% in the 1995 Mayo Clinic study with a mean follow-up of 6 years (range: 3 months to 18 years), 24% at ~2.8 years in the 2013 European series vs 3% at 3 years in the current account.[4,8]

Another unique aspect of this study stems from its comparison of select transcriptome targets in affected skin samples derived from a subset of patients with scleromyxedema to that of control skin samples derived from patients undergoing plastic surgery. Genes such as transforming growth factor-β and collagen 1a that are associated with the production of collagen, as well as interleukin-8 (IL-8) and IL-10 that are associated with an activated autoinflammatory pathway, were significantly higher in the affected skin samples from patients with scleromyxedema than in the control skin samples from healthy donors. However, contrary to expectations, no difference in the expression of the *CHSY1* gene that is related to mucin production was observed. These findings shed light on the potential therapeutic targets against the cutaneous symptoms observed in scleromyxedema.

In scleromyxedema, the size of the monoclonal protein is typically small and therefore vulnerable to false negative test results. Although in the French series, a monoclonal protein was detected across the entire cohort of 33 patients with the aid of conventional tools, "atypical cases" characterized by the absence of a monoclonal protein have been described. The availability of more sensitive and inexpensive technologies, such as the immunoglobulin enrichment coupled with matrix-assisted laser desorption ionization time-of-flight mass-spectrometry, may permit early recognition of patients, and therefore, early institution of therapies, thereby preventing disfiguring sequelae in patients suspected to have scleromyexedema.[9]

However, the current series, akin to its historical counterparts, is beleaguered by limitations on several fronts, outside of the inherent biases associated with retrospective studies. The subjects included were diagnosed over a 20-year interval during which the antimyeloma therapies have evolved considerably, and given the small overall sample size, delineation of the impact of individual plasma cell–directed therapies, with subset analyses is not feasible. Although a host of therapies was used, several newer, more potent agents, such as carfilzomib, pomalidomide, and daratumumab, were not employed, and their benefit remains unexplored. The disparateness of the patient populations across studies along with the heterogeneity of treatments used makes indirect comparisons rather challenging. The adequate duration of therapy, its deescalation during the maintenance phase of treatment, the use of doublet vs triplet combinations of drugs, the impact of combinations incorporating IVIG plus novel antimyeloma agents vs antimyeloma agents alone remain unknown. Moreover, the study lacks patient-reported outcomes and quality-of-life data, arguably substantially important parameters of ascertainment of clinical benefit in this disease. These deficiencies can only be successfully addressed through large international collaborative efforts.

Nonetheless, the study presents a comprehensive overview of the clinical aspects of a sizeable cohort of patients, underscoring the value of rapidly expanding therapeutic landscape and fostering hope among the ones afflicted by another rare condition governed, to a large extent, by "small dangerous B-cell clones."[10]

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