Idiopathic Systemic Capillary Leak Syndrome Preceding Diagnosis of Infiltrating Lobular Carcinoma of the Breast With Quiescence During Neoadjuvant Chemotherapy

To the Editor: A 43-year-old woman presented with 3 episodes of shock within a 6-month period (Table); all episodes occurred after symptoms of nonspecific abdominal pain. During the second episode of shock, an infiltrating lobular carcinoma of the breast (estrogen receptive–positive, progesterone receptor–negative, human epidermal growth factor 2–positive [T3,N1,M0]) was diagnosed. After resolution of the third episode of shock, a standard regimen consisting of paclitaxel, carboplatin, and trastuzumab was instituted; the patient had no further episodes of shock for the next 9 months.

Three months after the patient underwent a modified radical mastectomy and completed chemotherapy, she experienced 4 episodes of hypotension within a 3-week period, the last of which resulted in refractory shock. On the basis of her history of unexplained shock with prodromal symptoms and an IgG κ monoclonal gammopathy, idiopathic systemic capillary leak syndrome (SCLS) was diagnosed. Prophylactic therapy with terbutaline and theophylline was initiated. Eighteen months later, the patient experienced 1 episode of shock, with a concurrently low level of serum theophylline (7.7 μg/mL). In addition to resuscitation with 10 L of normal saline in the first 24 hours, she was given increasing doses of theophylline and treated with albumin infusion and montelukast; symptoms resolved after 1 day of this therapeutic regimen.

Idiopathic SCLS is a rare and life-threatening disorder, with only 100 to 125 cases published worldwide since the first report in 1960.[1-6] The shock that patients with SCLS experience, with associated hemoconcentration and hypoalbuminemia, is caused by sudden, massive leakage of proteins and serum into the extravascular space.[1,7] Plasma proteins up to 200 kDa or, in some cases, 900 kDa escape the capillary bed, resulting in an intravascular loss of up to 70% of plasma volume.[2,8,9] Most patients have an associated IgG κ or λ monoclonal gammopathy,[1,10] although its importance remains unknown.

Idiopathic SCLS has been reported preceding hematologic malignancy[11] but not in association with a solid tumor; it should be distinguished from drug-induced SCLS that may occur after treatment of other malignancies. In addition to the classic findings, our patient had neutrophilia at the outset of each attack, which lasted 24 to 48 hours and was as high as 40×10^9/L during one episode. Given that neutrophilia has been observed in patients with SCLS, it is notable that no episodes of SCLS occurred in our patient while receiving chemotherapy, and routine laboratory testing during that time revealed low or normal white blood cell counts. Demargination due to endothelial damage could be responsible for the neutrophilia, but a pathologic role of the neutrophils is also a possibility.

Although the mechanism behind capillary leak in idiopathic SCLS is unknown, evidence supports endothelial apoptosis, rather than endothelial contraction or widened cell-cell junctions, as the cause.[1,13,14] Use of numerous investigational drugs has been reported with variable outcomes.[6,15-20] Traditional prophylactic therapies, theophylline/aminophylline and terbutaline, have been reported to achieve durable success,[3,6,9,21] despite a lack of understanding of their mode of action. Spironolactone, hydrocortisone, progesterone, and dexamethasone all appear to protect against endothelial cell apoptosis in response to serum deprivation,[22] whereas albumin inhibits endothelial cell apoptosis when there is intact endothelial cell adhesion,[23] suggesting that these therapies have potential benefit.

Neutrophil-mediated endothelial apoptosis has been described in patients with other inflammatory disorders.[24,25] Given the neutrophilia seen in SCLS and the quiescence of SCLS in our patient while receiving neoadjuvant chemotherapy, one area of interest may involve neutrophil regulation. Although the chemotherapeutic benefit may have been due

TABLE. **Laboratory Values at Patient Presentation of Each Episode of Shock**[a]

	Episode				
	1	2	3	4	5
WBC[b] ($\times 10^9$/L)	…	22.0[c]	16.1[c]	10.6[c]	11.0[c]
ANC[b] ($\times 10^9$/L)	…	15.7[c]	10.3[c]	9.24[c]	8.0[c]
Hemoglobin[b] (g/dL)	…	18.3[c]	19.1[c]	14.6	19.5[c]
ESR (mm/h)	…	…	13	…	…
CRP (mg/dL)	…	<0.1	0.3	…	…
TSH (mIu/L)	…	2.99	1.68	…	…
IgA (mg/dL)	…	69[c]	…	29[c]	…
IgE (U/mL)	…	<3.0[c]	<3.0[c]	…	…
IgM (mg/dL)	…	76	…	28[c]	…
IgG (mg/dL)	…	652[c]	…	457[c]	…
c-ANCA	…	Negative	…	…	…
p-ANCA	…	Negative	…	…	…
ANA	…	…	Negative	…	…
Celiac panel[d] (IgG Ttg, IgA Ttg, IgA endomysial Ab)	…	Negative	…	…	…
Paraneoplastic Ab[e]	…	…	Negative	Negative	…
C2 complement (mg/dL)	…	…	0.7[c]	…	…
C3 complement (mg/dL)	…	…	40[c]	40[c]	…
C4 complement (mg/dL)	…	…	11[c]	11[c]	…
C5 complement (mg/L)	…	…	108	…	…
VEGF (pg/mL)	…	…	…	…	55

[a] No data available for the patient's first episode of shock, which was managed at another institution. Ab = antibody; ANA = antinuclear antibody; ANC = absolute neutrophil count; c-ANCA = cytoplasmic antineutrophil cytoplasmic antibody; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; p-ANCA = perinuclear antineutrophil cytoplasmic antibody; TSH = thyroid-stimulating hormone; VEGF = vascular endothelial growth factor; WBC = white blood cell count.

[b] WBC, ANC, and hemoglobin values are those on admission.

[c] Abnormal values.

[d] Anti-tissue transglutaminase (Ttg) Ab testing was performed to rule out celiac disease as a cause of abdominal pain.

[e] Paraneoplastic Ab testing was performed to address possible autonomic dysfunction as a result of a paraneoplastic syndrome due to the breast cancer.

to general immunosuppression, there may be mechanism-specific similarities between theophylline, paclitaxel, and carboplatin. In addition to decreasing endothelial permeability through elevation of intracellular cyclic adenosine monophosphate[5,26] and offering immune-modulatory effects,[26] theophylline may affect neutrophil life span. Theophylline causes granulocyte apoptosis in vitro, even in the presence of granulocyte-macrophage colony-stimulating factor,[27] with B-cell lymphoma 2 (bcl-2) down-regulation involved in theophylline-induced apoptosis of eosinophilic granulocytes.[28] Granulocyte life span is determined by a balance of proapoptotic and antiapoptotic gene expression, with down-regulation of the inducible and short-lived anti-apoptotic bcl-2 family member expression sufficient for neutrophil apoptosis.[29,30] Both paclitaxel and carboplatin also affect bcl-2 down-regulation in other settings.[31,32] Given these observations, future studies should investigate whether neutrophils obtained during acute attacks are sufficient to cause endothelial apoptosis, whether bcl-2 or its family members are aberrantly expressed, and whether the aforementioned drugs alter bcl-2 family member expression.

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