**Improved Metastatic Uterine Papillary Serous Cancer Outcome With Treatment of Mast Cell Activation Syndrome**

**The Case:** In May 2010, a 71-year-old woman not on hormone replacement therapy presented with uterine bleeding. Endometrial biopsy was foiled by severe cervical stenosis. Dilation & curettage revealed complex hyperplasia with atypia, focal clear-cell features, and endocervicitis. Endometrial intraepithelial carcinoma was suspected. Frozen section analysis from hysterectomy and bilateral salpingo-oophorectomy revealed noninvasive grade 1 endometrial cancer. Thus, lymphadenectomy was not performed. However, final pathology showed metastatic uterine papillary serous adenocarcinoma (UPSC) with bilateral tubo-ovarian micrometastases. Additional testing showed microsatellite instability but not Lynch syndrome. Positron emission and computed tomography (PET/CT) in August 2010 demonstrated hypermetabolic adenopathy, including a 1.1-cm para-aortic node (fluorodeoxyglucose [FDG] standardized uptake value [SUV] of 3.4), a subcentimeter aortocaval node (SUV , 2.4), and a 1.0-cm node inferior to the aortic bifurcation (SUV, 2.7). Cancer antigen 125 (CA-125) level was 55.9 U/mL.

The patient declined full surgical staging, including pelvic/para-aortic lymphadenectomy. She began carboplatin and paclitaxel (CP), which was well tolerated until superficial venous thrombosis of the right distal great saphenous and right small saphenous veins during cycle 4. Warfarin was started. Restaging PET/CT in December 2010 after cycle 6 demonstrated progression of prior metastatic disease (multiple para-aortic nodes up to 1.2 cm, with SUV of 8.6) and new metastatic disease (external iliac adenopathy up to 0.9 cm, with SUV of 4.7; and paraatracheal adenopathy up to 1.3 cm, with SUV of 4.3).

She was started on salvage paclitaxel, doxorubicin, and cisplatin (TAP). In light of her son’s alleged protein S deficiency, she was referred for hematologic consultation; only a modest lupus anticoagulant level was found. Anticoagulation was switched to enoxaparin because of an unstable warfarin response. She was more symptomatic with TAP, reporting abdominal bloating, presyncopal episodes and palpitations (worst in each cycle’s second week, once she was off dexamethasone), soaking sweats, nausea, polyuria, polydipsia, grade 1 peripheral neuropathy, left hip pain on movement, heartburn, constipation, fatigue, and dyspnea, all of which progressed through treatment. Post–cycle 3 PET/CT in March 2011 showed new subpectoral adenopathy (1.7 cm; SUV, 8.2) and a mixed response at other sites (eg, paraaortic adenopathy up to 1.0 cm, SUV of 3.6; paraatracheal adenopathy up to 1.5 cm, SUV of 3.3). Diversitulitis in the sigmoid colon was seen and was treated with amoxicillin/clavulanic acid. Abdominal pain improved somewhat. The CA-125 level, which had decreased after the first CP cycle to 24.2 U/mL, was now 15.3 U/mL. TAP was continued. Post–cycle 5 PET/CT in May 2011 again showed a mixed response (eg, subpectoral adenopathy of 1.2 cm × 0.7 cm, SUV of 1.1; paraatracheal adenopathy of 1.5 cm, SUV of 3.5; para-aortic adenopathy of 0.6 cm in the short axis, SUV of 1.0). Diversitulitis has resolved. CA-125 reached its lowest level, at 6.9 U/mL, after cycle 7. Post–cycle 8 PET/CT in August 2011 showed minor further response (subpectoral adenopathy of 0.3 cm in the short axis, SUV of 0.6; paraatracheal adenopathy of 1.5 cm, SUV of 2.2; para-aortic adenopathy of 0.5 cm in the short axis, SUV of 0.9).

Chemotherapy was stopped. Medroxyprogesterone (MP) at 40 mg twice daily was started. The patient soon noticed worsened fatigue. During evaluation of presyncope in August 2011, she reported many chronic issues. These included hot flashes; chills; migratory pruritus; mild visual anomalies; excessive lacrimation, chronic coryza, and postnasal drip; heartburn; episodic documented hypotension; and life-long unprovoked episodes of hypomania. Mast cell activation disease (MCAD) was considered as a unifying diagnosis. Testing was delayed, but she began a full histamine blockade (famotidine, 40 mg twice daily, and loratadine, 10 mg twice daily); also, enoxaparin was stopped and daily aspirin was increased from 81 mg to 325 mg. Her symptoms all resolved. A month later she stopped aspirin and antihistamines for mast cell (MC) mediator testing. Her symptoms all immediately returned. After testing, she resumed aspirin and antihistamines, and she re-achieved complete remission of her symptoms within a week. Her serum trypsin level was normal, but her serum prostaglandin D2 (PGD2) level was mildly elevated (128 pg/mL [normal, 35–115 pg/mL]), her plasma heparin level was mildly elevated (anti-factor Xa, 0.040 U/mL [normal, 0.000–0.020 U/mL]), and her factor VIII level was moderately elevated (273% [normal, 50% to 150%]).

In view of the clinical history consistent with chronic aber-
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Discussion
This appears to be the first reported case of metastatic UPSC refractory to two lines of chemotherapy, which then responded well after comorbid MCAS was recognized and treated. UPSC is an aggressive postmenopausal nonendometrioid uterine cancer that is often chemoresistant from onset, with low response rates, short response durations, and a 5-year survival rate of 18% for stage IV disease;[2-5] even worse outcomes are expected with disease resistant to two lines of chemotherapy. The relationship between peritumoral MCs and uterine cancer is complex, as reflected in contrasting pathologic studies,[6-8] and MC disease per se has not previously been reported in association with uterine cancer. However, some have suggested that MC-targeted treatment might be a helpful adjunct.[6,7]

Some of our patient’s symptoms that emerged during TAP therapy may have been due to chemotherapy. However, the full range of her symptoms (some of which long preceded the emergence of her cancer) was poorly explained by her cancer, other comorbidities, or cancer therapies, and some of them instead were potentially consistent with MC activation. The normal serum tryptase level suggested that SM was unlikely, and no increase in MCs was seen on pathologic re-examination of her tumor (Figure). Other MC mediator tests, however, confirmed MC activation, and her symptoms—many of which are classic symptoms of MC disease (eg, flushing, pruritus, vasomotor instability)—responded well to MCAS-targeted therapy, reappeared when she was off such therapy, and responded again to resumption of therapy.

Her 2+ years of post-treatment survival and good control of an ordinarily aggressive cancer are unusual and not likely due exclusively to cancer treatment. While the decreases in size and FDG avidity of her (presumably metastatic) adenopathy might be from chemotherapy, the timing of these improvements was poorly correlated with her chemotherapy, with some worsening of adenopathy occurring well into the second line of chemotherapy, and improvements in adenopathy continuing months after her last chemotherapy treatment.

Waxing/waning adenopathy is a feature of MC disease.[9] It is possible that the patient's adenopathy was a mixture of tumor and MCAS-driven inflammation, and that a combination of chemotherapy and MCAS-directed therapy produced the complicated, overall improved response seen over time. Also, some of her other inflammatory and fibrotic issues may have been partly driven by acute and chronic effects of her MCAS. Of hematopoietic origin, MCs are present in every human tissue but preferentially site themselves at environmental interfaces to better perform their principal function as sentinels against environmental insults.[10,11]

There are more than 200 MC mediators, each with a unique array of direct and indirect, local and remote effects. [12] MCAD—the new umbrella term for MC disease, encompassing both the long-recognized but rare mastocytosis...
sis[13-15] and the recently recognized and possibly quite prevalent MCAS[15,16]—often presents with chronic multi-system polymorbidity of a generally inflammatory nature,[1,9] and this can aggravate the risk and course of cancer.[17] MCAD often contributes to unusual presentations and courses of comorbidities. For example, it is possible that our patient’s MCAD may have contributed to her tumor’s microsatellite instability, rarely seen in UPSC.[18] In spite of its suspected prevalence, the recent recognition of MCAS (first cases published in 2007[19-21]) and its heterogeneous, multisystem presentations (Table)—often masked by more flagrant clinical problems, as in our patient—pose significant diagnostic challenges.

Slightly varying systems of diagnostic criteria for MCAS have been proposed by different groups,[1,22,23] and include a history consistent with aberrant MC mediator release; the

| Table | Symptoms and Findings in MCAD
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<tr>
<td>System</td>
<td>Potential Manifestations of MCAD</td>
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<tr>
<td>Constitutional</td>
<td>Fatigue, subjective or objective hyperthermia and/or hypothermia, sweats, flushing, plethora or pallor, increased or decreased appetite, weight gain or loss, pruritus, chemical/physical sensitivities (often odd), poor healing</td>
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<tr>
<td>Dermatologic/ integument</td>
<td>Rash/es of many sorts (eg, classic urticaria pigmentosa, telangiectasias, xerosis, striae, warts, tags, folliculitis, ulcers, dyshidrotic eczema, migratory but sometimes focally persistent patchy macular erythema, migratory pruritus (sometimes aquagenic), angioedema, dermatographism, alopecia, onychodystrophy</td>
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<tr>
<td>Ophthalmologic</td>
<td>Irritated eyes, episodic difficulty focusing, lid tremor/tic (blepharospasm)</td>
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<td>Otologic/osmic</td>
<td>Infectious or sterile otitis externa and/or media, hearing loss and/or tinnitus, dysosmia, coryza, congestion, epistaxis.</td>
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<tr>
<td>Oral/ oropharyngeal</td>
<td>Pain or irritation (sometimes “burning”), leukoplakia, ulcers, angioedema, dysgeusia, dental or periodontal inflammation/decay</td>
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<tr>
<td>Lymphatic</td>
<td>Adenopathy (usually subpathologic and spontaneously waxing/waning in size, sometimes migratory), adenitis, splenitis</td>
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<tr>
<td>Pulmonary</td>
<td>Airway inflammation at any or all levels, cough, dyspnea (usually mild, episodic, and accompanied by normal pulmonary function tests), wheezing, obstructive sleep apnea, pulmonary hypertension</td>
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<td>Cardiovascular</td>
<td>Presyncope or syncope, hypertension and/or hypotension, palpitations, migratory edema, chest pain (usually nonanginal), atherosclerosis, odd heart failure (eg, takotsubo), allergic angina (Kounis syndrome), vascular anomalies</td>
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<tr>
<td>Gastrointestinal</td>
<td>Dyspepsia, reflux, nausea, vomiting (sometimes cyclical), diarrhea and/or constipation (often alternating), angioedema, dysphagia (often proximal), bloating/gas, migratory abdominal pain from luminal or solid organ inflammation, malabsorption, ascites</td>
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<tr>
<td>Genitourinary</td>
<td>Migratory luminal and solid organ inflammation, chronic kidney disease, endometriosis, chronic back/flank/ abdominal pain, infertility, decreased libido; miscarriages may signal an MCAS-rooted antiphospholipid antibody syndrome</td>
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<tr>
<td>Musculoskeletal</td>
<td>Migratory bone/joint/muscle pain, joint laxity/hypermobility, osteopenia and/or osteosclerosis</td>
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<tr>
<td>Neurologic</td>
<td>Headache, sensory, and/or motor neuropathies, seizure disorders, pseudoseizures, dysautonomia</td>
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<tr>
<td>Psychiatric</td>
<td>Mood disturbances, anxiety/panic, psychoses, cognitive dysfunction (most commonly memory and word-finding difficulties), sleep disruption</td>
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<tr>
<td>Endocrinologic/ metabolic</td>
<td>Abnormal electrolytes and liver function tests, hypothyroidism, hyperthyroidism, dyslipidemia, impaired glucose control, hyperferritinemia, nutritional deficiencies, delayed puberty, dysmenorrhea</td>
</tr>
<tr>
<td>Hematologic/ coagulopathic</td>
<td>Polycythemia or anemia (macrocytic, normocytic, or microcytic), leukocytosis or leukopenia, monocytes/ eosinophila/basophilia, thrombocytosis or thrombocytopenia, arterial and/or venous thromboembolic disease, otherwise inexplicable “easy” bruising/bleeding; usually no histologic or molecular evidence of MC aberrancy in the marrow in MCAS</td>
</tr>
<tr>
<td>Immunologic</td>
<td>Hypersensitivity reactions, increased risk for malignancy and autoimmunity, impaired healing, increased susceptibility to infection, increased or decreased levels of immunoglobulin of any isotype, monoclonal gammopathy of undetermined significance</td>
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Most symptoms are chronic and low-grade; some are persistent, many are either episodic or waxing/waning. More comprehensive lists and discussions are available.

MC = mast cell; MCAD = mast cell activation disease; MCAS = mast cell activation syndrome. Data from: Afrin L. Presentation, diagnosis, and management of mast cell activation syndrome. In: Murray D. Mast cells: phenotypic features, biological functions, and role in immunity. 2013.[9]
Improved Metastatic Uterine Papillary Serous Cancer Outcome With Treatment of Mast Cell Activation Syndrome

continued from page 131

presence of elevated MC markers in blood or urine; response to empiric MC-directed therapy; and an absence of other known causes of MC activation, such as SM, allergy, or physical urticaria. A detailed guide to the diagnosis of MCAD has recently been published.[24]

In contrast to cytoproliferative mastocytosis, MCAS is a relatively nonproliferative disease, and since the serum tryptase level is now recognized as reflecting total body MC load far more than total body MC activation state, it is elevated little to none in MCAS, in contrast to significantly elevated levels in SM.[1,23] Symptoms of aberrant MC mediator release are none in MCAS, in contrast to significantly elevated levels in other relationship with the manufacturer of any product or provider of any service mentioned in this article.

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REFERENCES