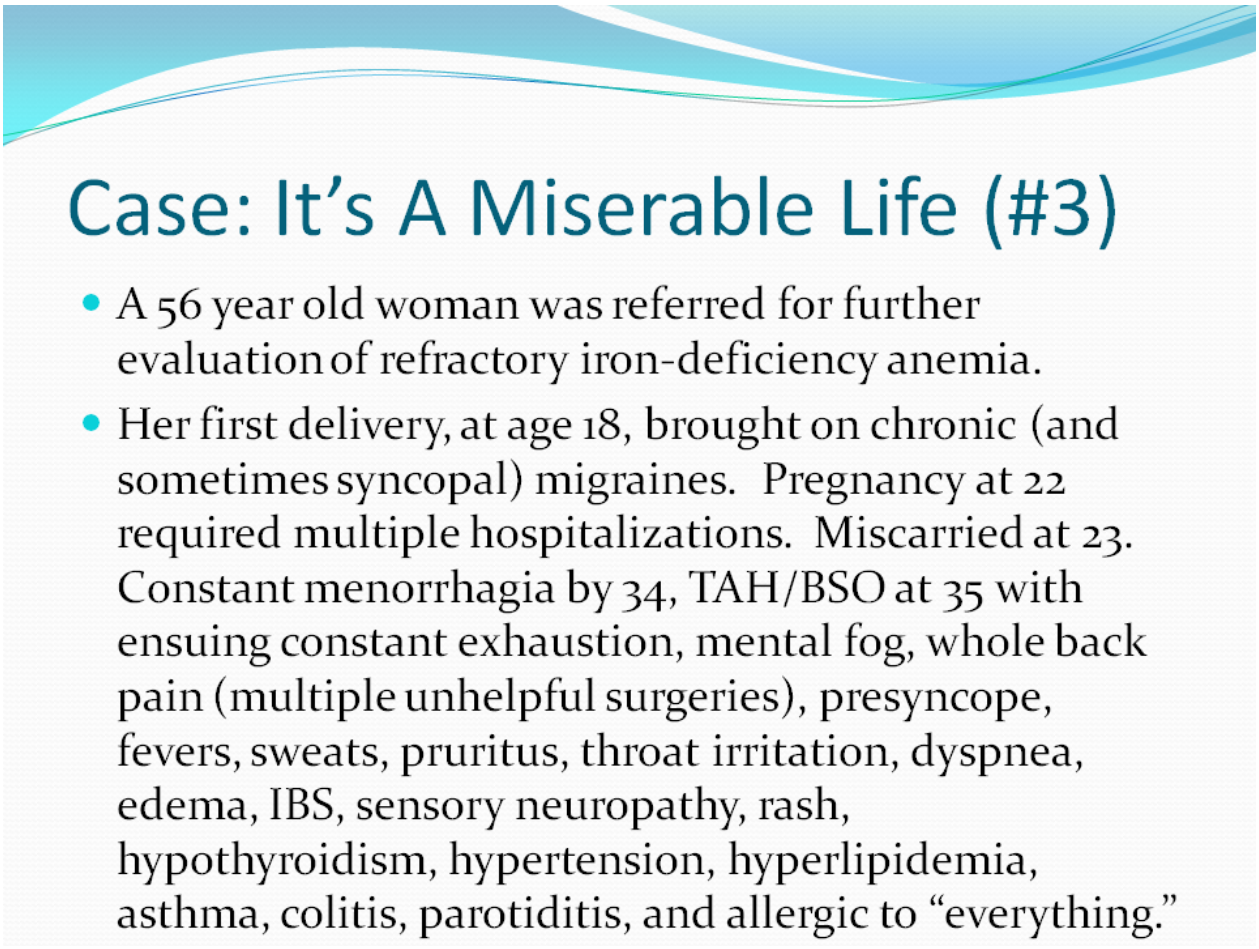
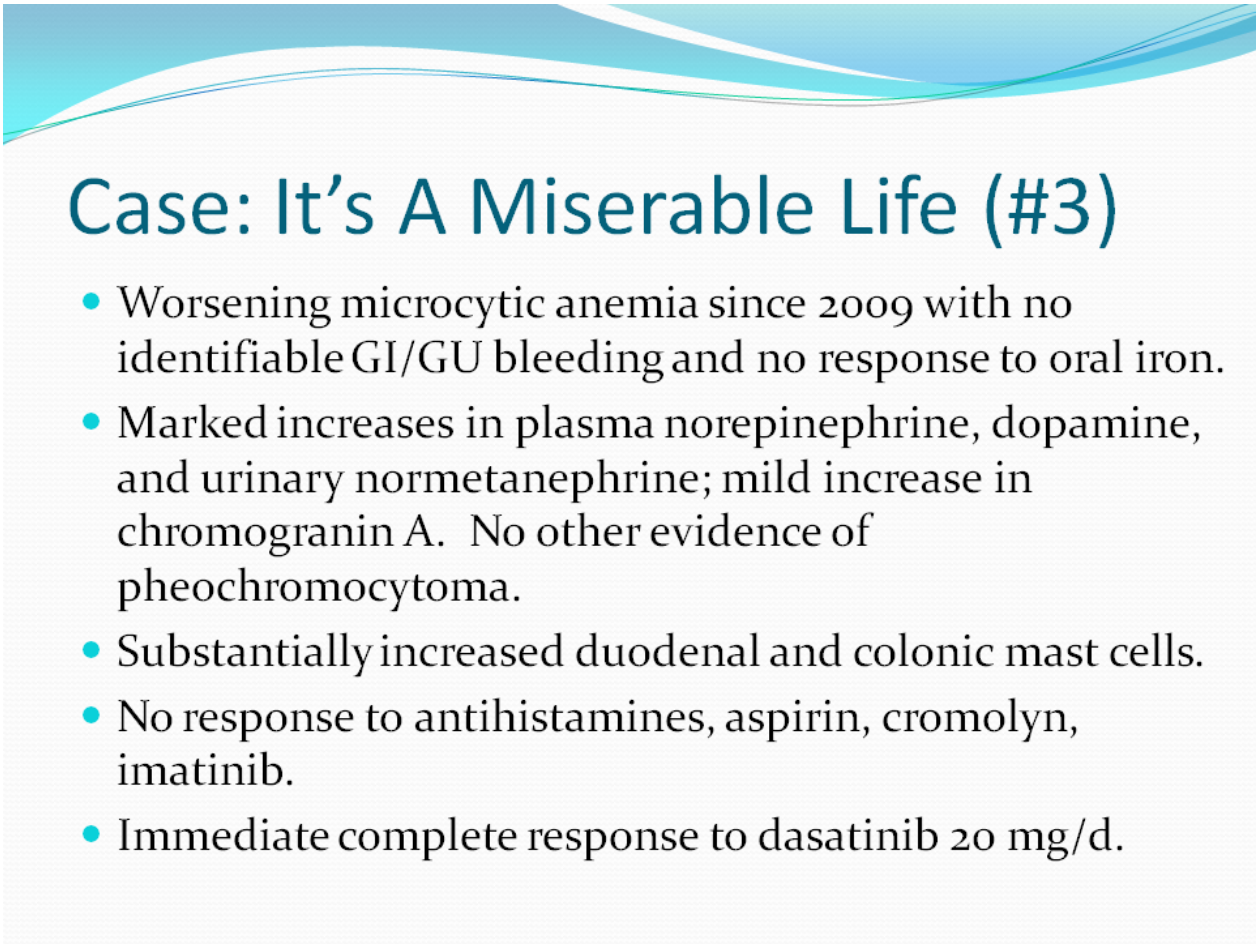
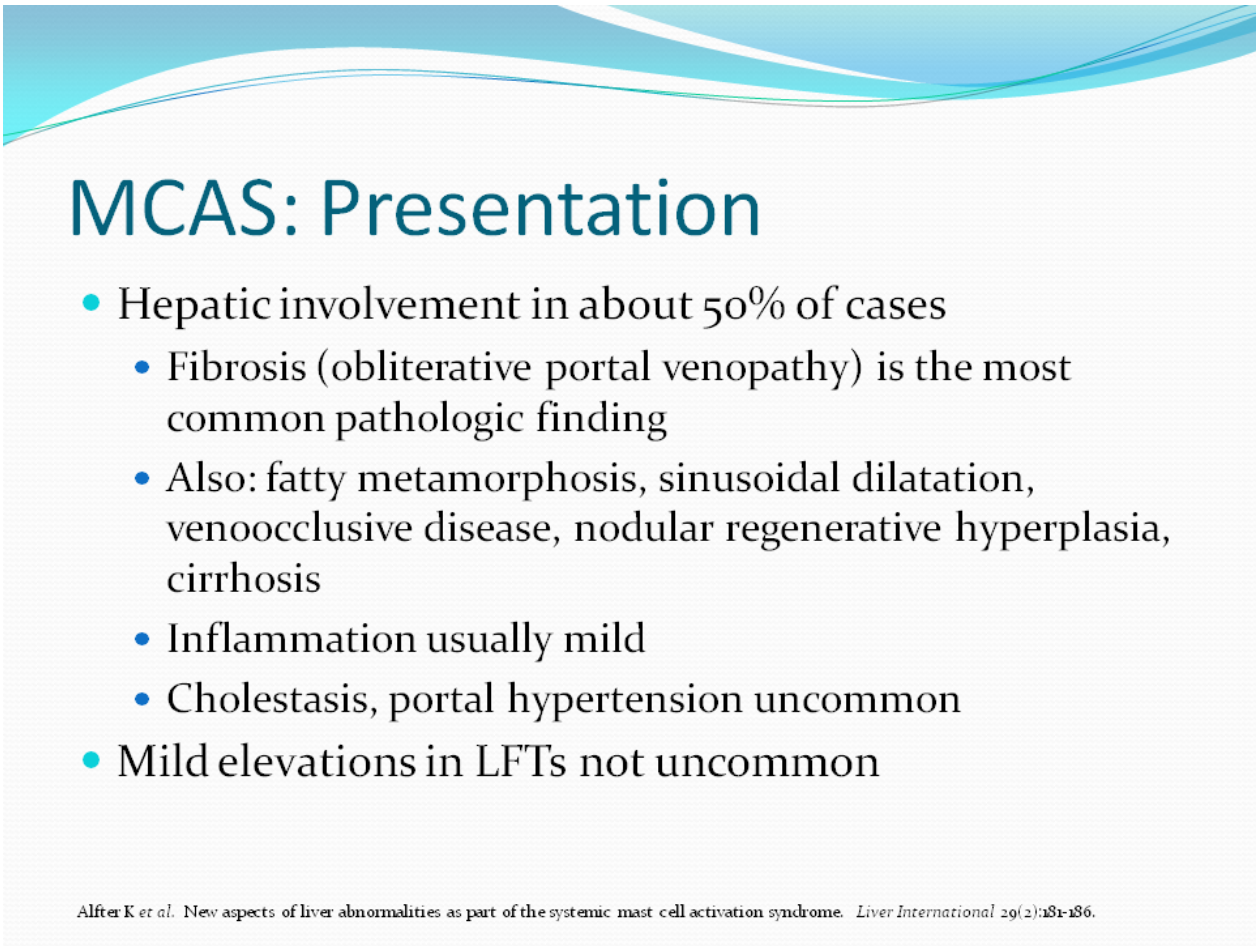
[Slides 60-61: Case: It's a Miserable Life (#3).]





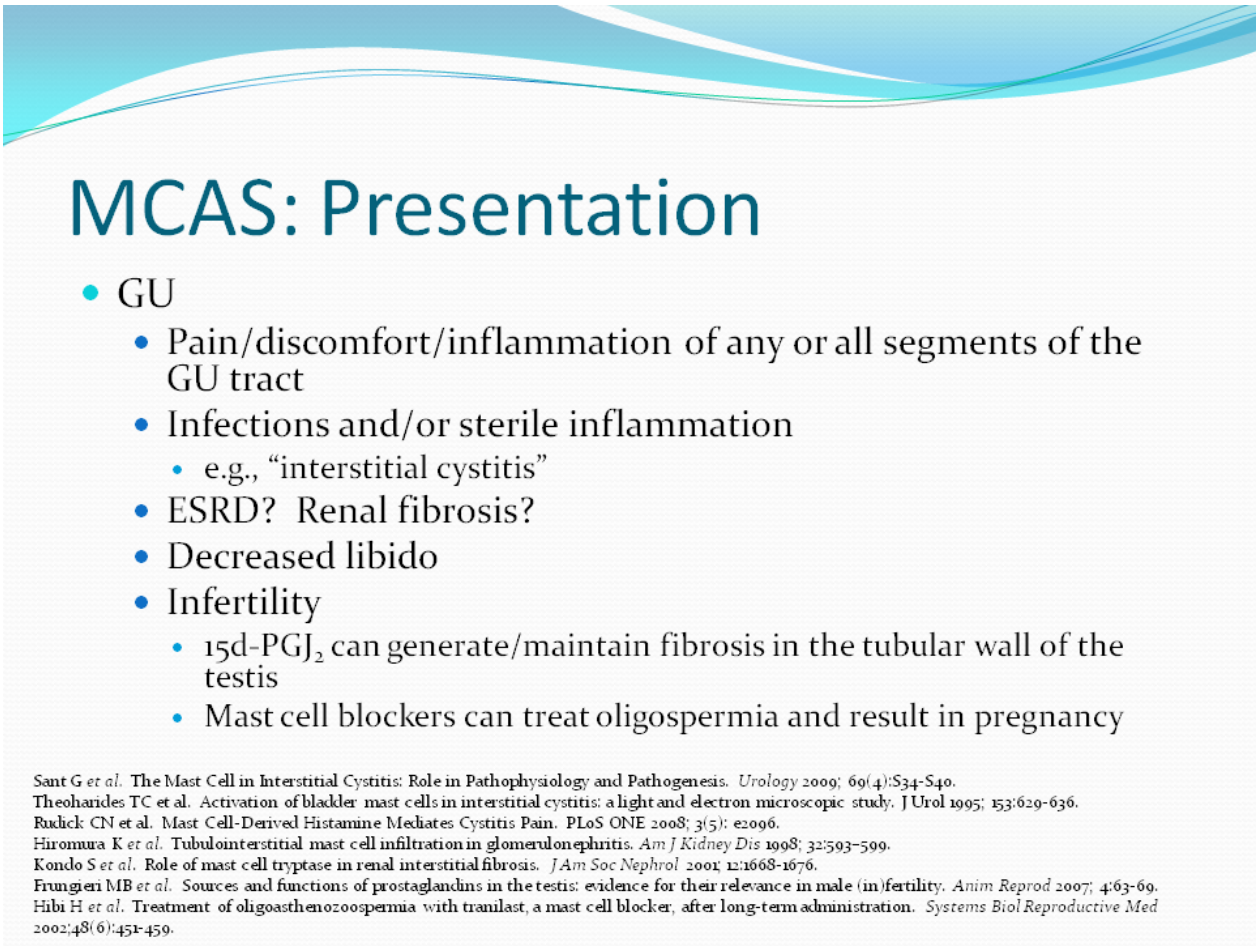
A 56 year old woman was referred for further evaluation of refractory iron-deficiency anemia. Her first pregnancy at age 18 brought on a number of obstetric complications and chronic migraines, and many other problems developed over the years since, including eventually becoming allergic to seemingly everything. She then was noted to develop worsening microcytic anemia since 2009 with no identifiable bleeding. An oral iron absorption test showed deficient absorption. She also had marked increases in catecholamines in the blood and urine, mild increase in serum chromogranin A, no evidence of pheochromocytoma or carcinoid, and substantially increased GI mast cells. She had no response to a number of agents we tried initially, but then we put her on low-dose dasatinib and – I am not making this up – she literally danced into the exam room in my clinic for her next checkup. Her improvement has been sustained for several months now. She actually does have one side effect from the dasatinib. She has had a mild headache from it, and I'm trying to deal with that. I'm trying to figure out how can I get her on an even lower dose of disatinib. They don't make a dose any lower than what she's on, and I can't find a pharmacist who is willing to cut such a tiny, expensive pill. So I'm not quite sure how to solve her dasatinib headache problem, but I guess that's not too big a problem at this point compared to all her trouble previously

[Slide 62: MCAS: Presentation.]



Hepatic issues in general are common, but what you'll see most commonly in this area by far is just a mild elevation in one transaminase and/or the other, often also with a mild elevation in alkaline phosphatase without an elevation in the bilirubin. This is a pattern often seen with "metabolic syndrome." Nobody knows what causes "metabolic syndrome," and I have been wondering whether "metabolic syndrome," too, might be another presentation of MCAS.

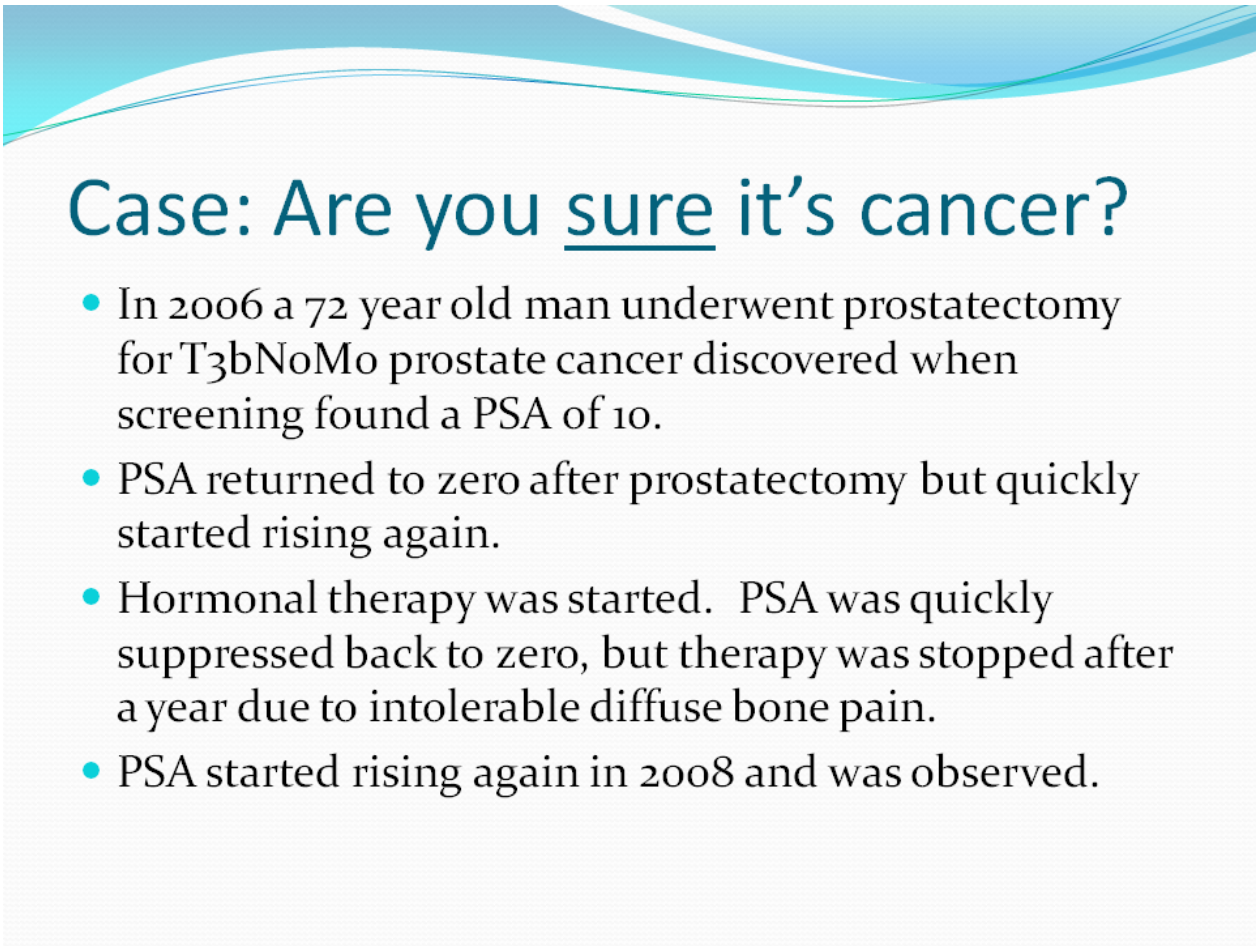
[Slide 63: MCAS: Presentation.]

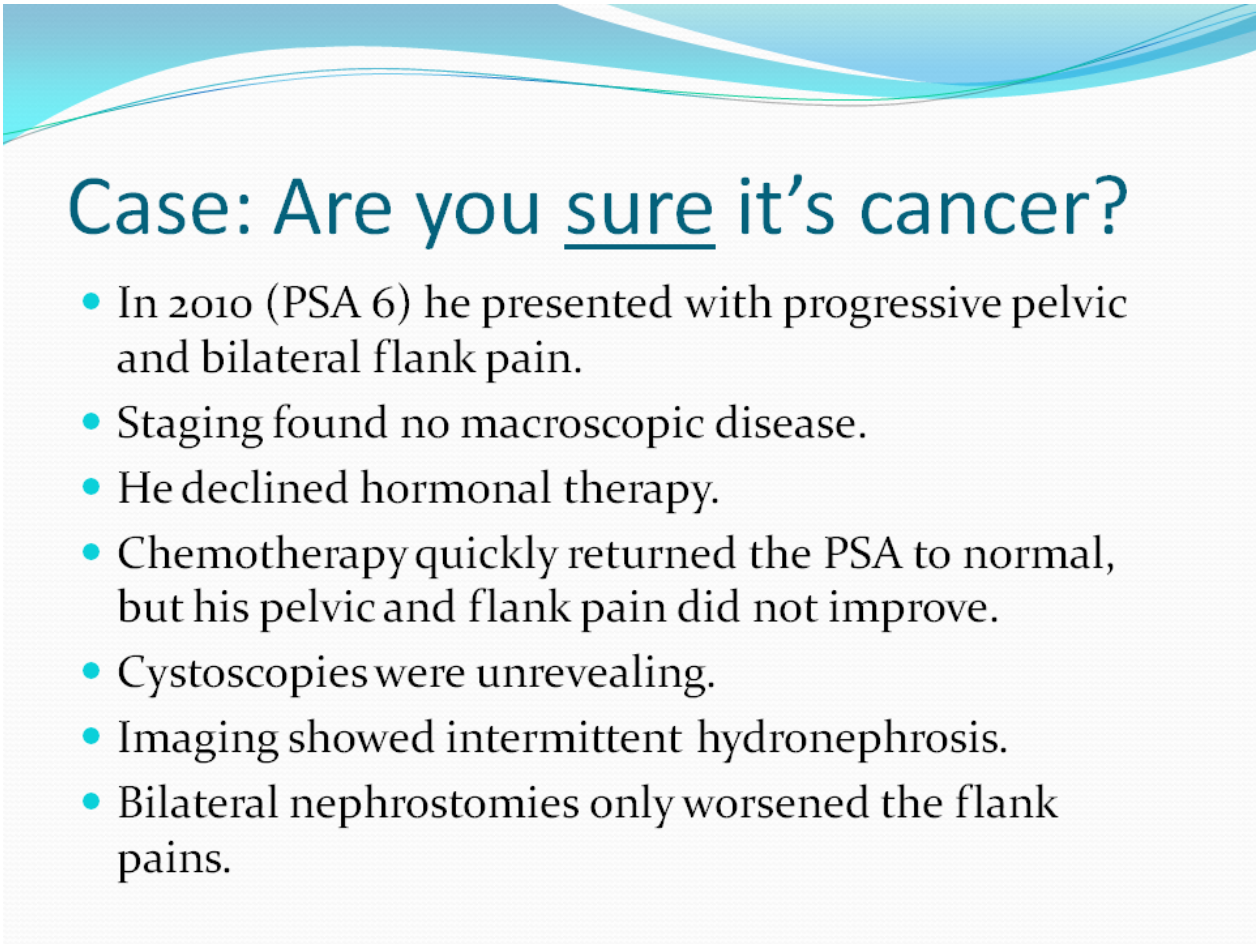


The GU issues, again, revolve around inflammation, but GU inflammation can be hard to recognize. These patients often present with chronic, migratory, waxing/waning, low-back/flank/pelvic pain. They also often present with frequent urinary tract "infections" except that actual proof of infection is rare. The cultures just keep coming back negative.

The disease can clearly impact the kidneys, libido, and fertility.

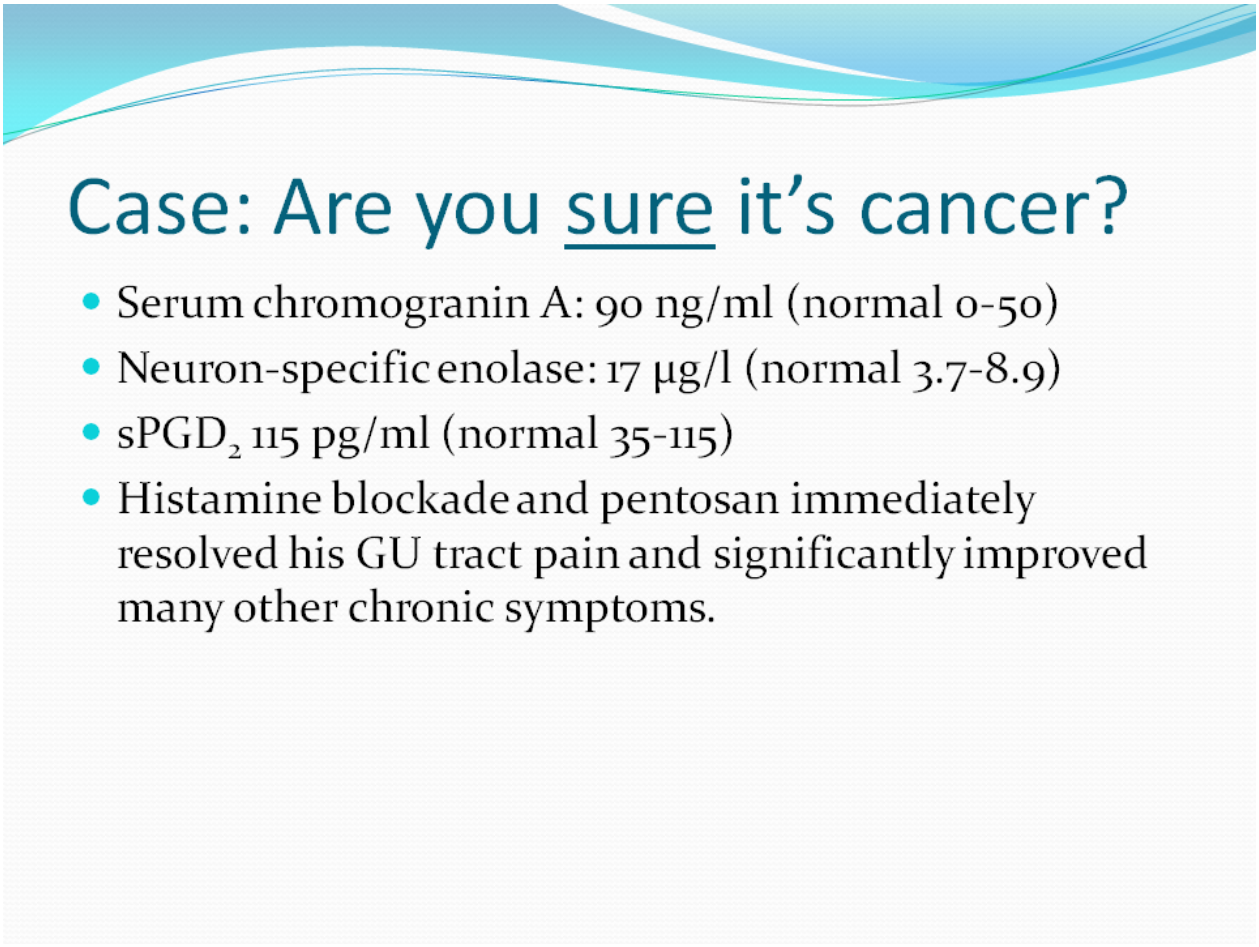
[Slides 64-67: Case: Are you sure it's cancer?]




Case: Are you sure it's cancer?
In 2010 (PSA 6) he presented with progressive pelvic and bilateral flank pain.
Staging found no macroscopic disease.
He declined hormonal therapy.
Chemotherapy quickly returned the PSA to normal, but his pelvic and flank pain did not improve.
Cystoscopies were unrevealing.
Imaging showed intermittent hydronephrosis.
Bilateral nephrostomies only worsened the flank pains.

Case: Are you sure it's cancer?

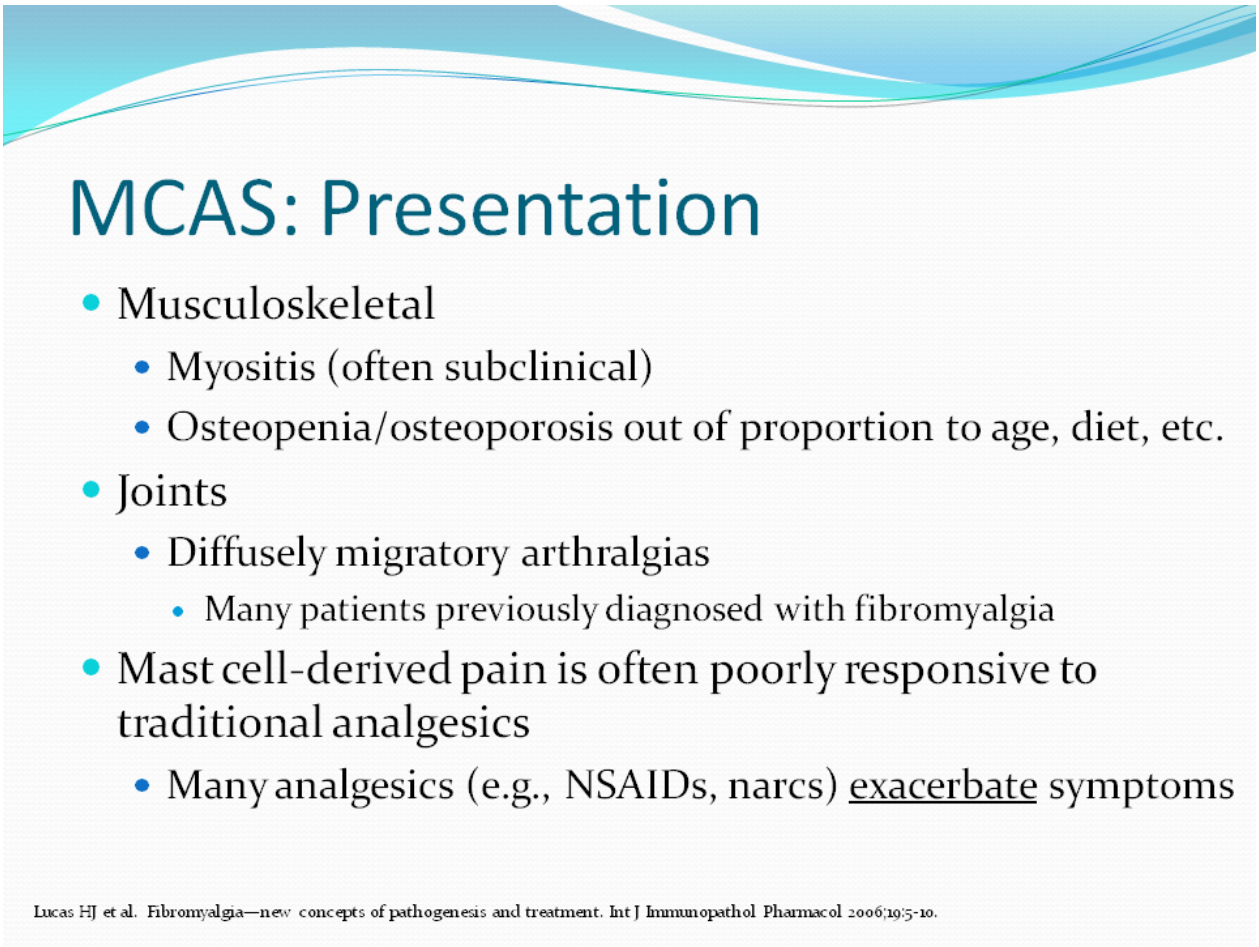
- Additional PMH/ROS found multiple problems since at least 1990: chronic fatigue, fibromyalgia, presyncope, urinary hesitancy, headache, chills, sweats, pruritus, proximal dysphagia, insomnia, anxiety, depression, nightmares, absent libido, erectile dysfunction, eye and throat irritation, dyspnea, non-anginal chest pain, constipation, refractory GERD, cognitive dysfunction, sensory neuropathy, hypertension, asthma, and multiple odd medication sensitivities.



In 2006 a 72 year old man underwent prostatectomy for what was called a locally advanced prostate cancer discovered when a screening prostate specific antigen (PSA) was modestly elevated at 10 ng/ml. His prostate was removed and his PSA quickly returned to zero, but then it quickly started rising again, which is a fairly common scenario with localized prostate cancer. Hormonal therapy was started, and the PSA dropped back to zero, but he couldn't tolerate the therapy and stopped it. His PSA started rising again, but initially he was just observed. In 2010 his PSA was still at a very modest 6 ng/ml when he presented with progressive pelvic and bilateral flank pain. There was no detectable evidence of prostate cancer beyond the PSA, but there was no other apparent explanation for his pain. So the team of oncologists treating his prostate cancer decided this PSA elevation must be prostate cancer, and he was started on chemotherapy which did knock the PSA back down to zero, but his pain did not improve – a situation akin to the MCAS-induced polycythemia case. He also had mysterious intermittent hydronephrosis of no identifiable cause. When I first took his history, a bevy of issues ongoing for 20 years emerged. Serum chromogranin A was elevated. PGD_2 was top end of normal. Histamine blockade and pentosan (a mast cell stabilizer helpful with GU tract disease) immediately resolved his pain and significantly improved many other chronic symptoms. I suspect what had been causing the episodic hydronephrosis

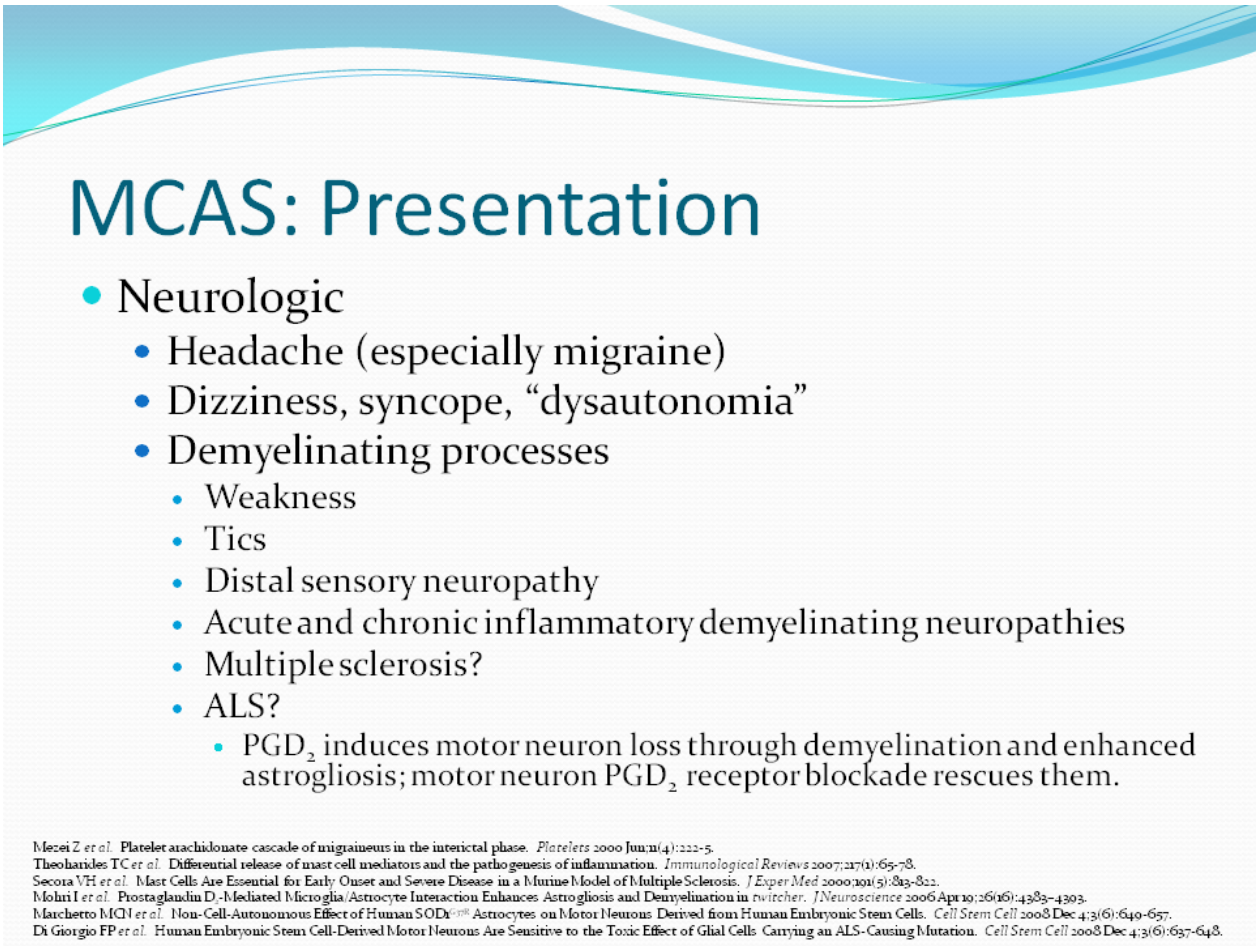
was flaring of ureteral mast cell disease causing ureteral edema to the point of obstruction.

[Slide 68: MCAS: Presentation.]



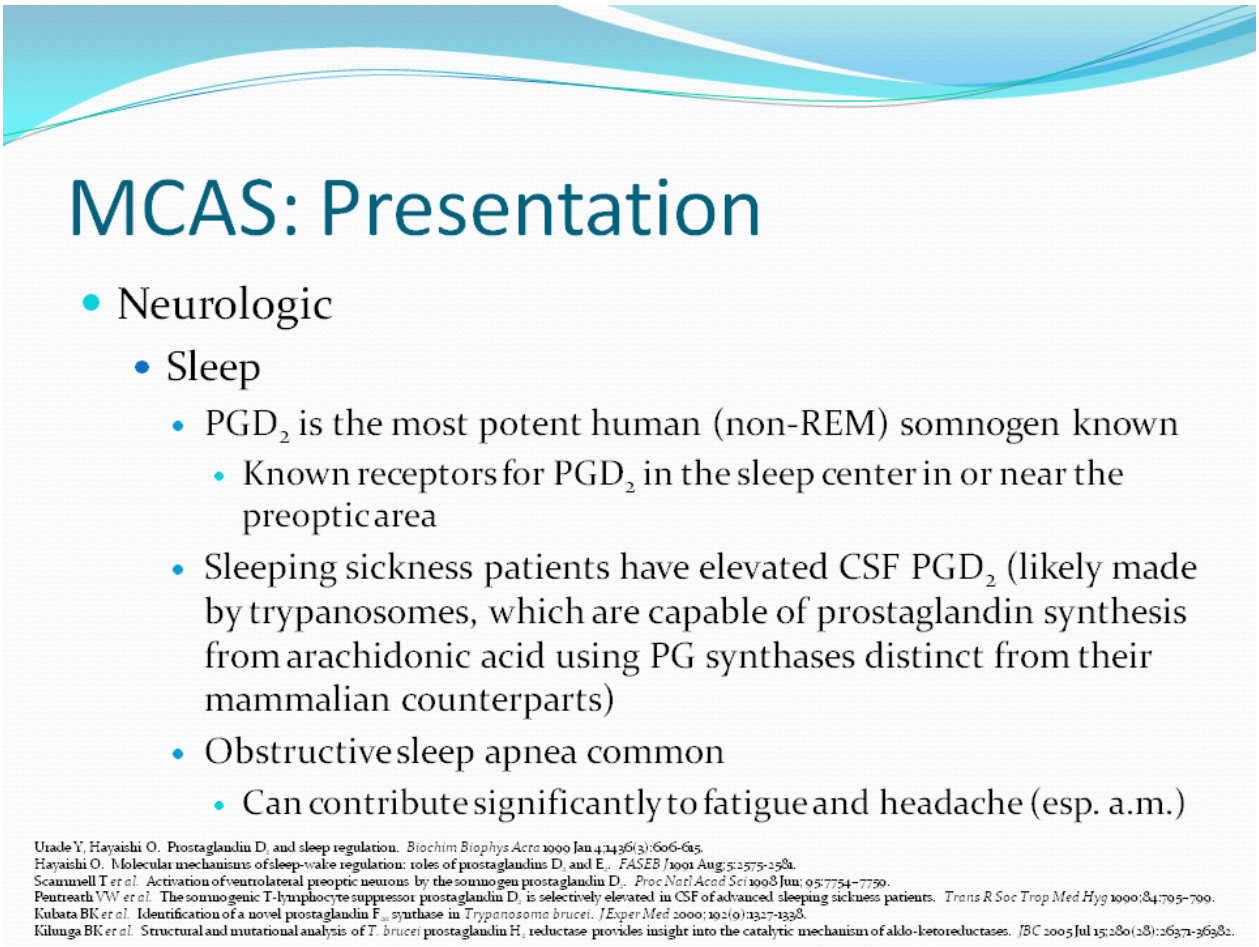
Unsurprisingly, there's a broad range of musculoskeletal issues in MCAS, too, including osteopenia (thinning of the bones) or osteroporosis out of proportion to age or diet. Also, these patients sometimes will have an elevated creatine kinase and/or elevated aldolase despite having no muscle symptoms at all. Other symptoms include diffusely migratory arthralgias. Many MCAS patients have been diagnosed previously with "fibromyalgia." They often poorly respond to all traditional analgesics (painkillers), which actually can make them worse.

[Slide 69: MCAS: Presentation.]



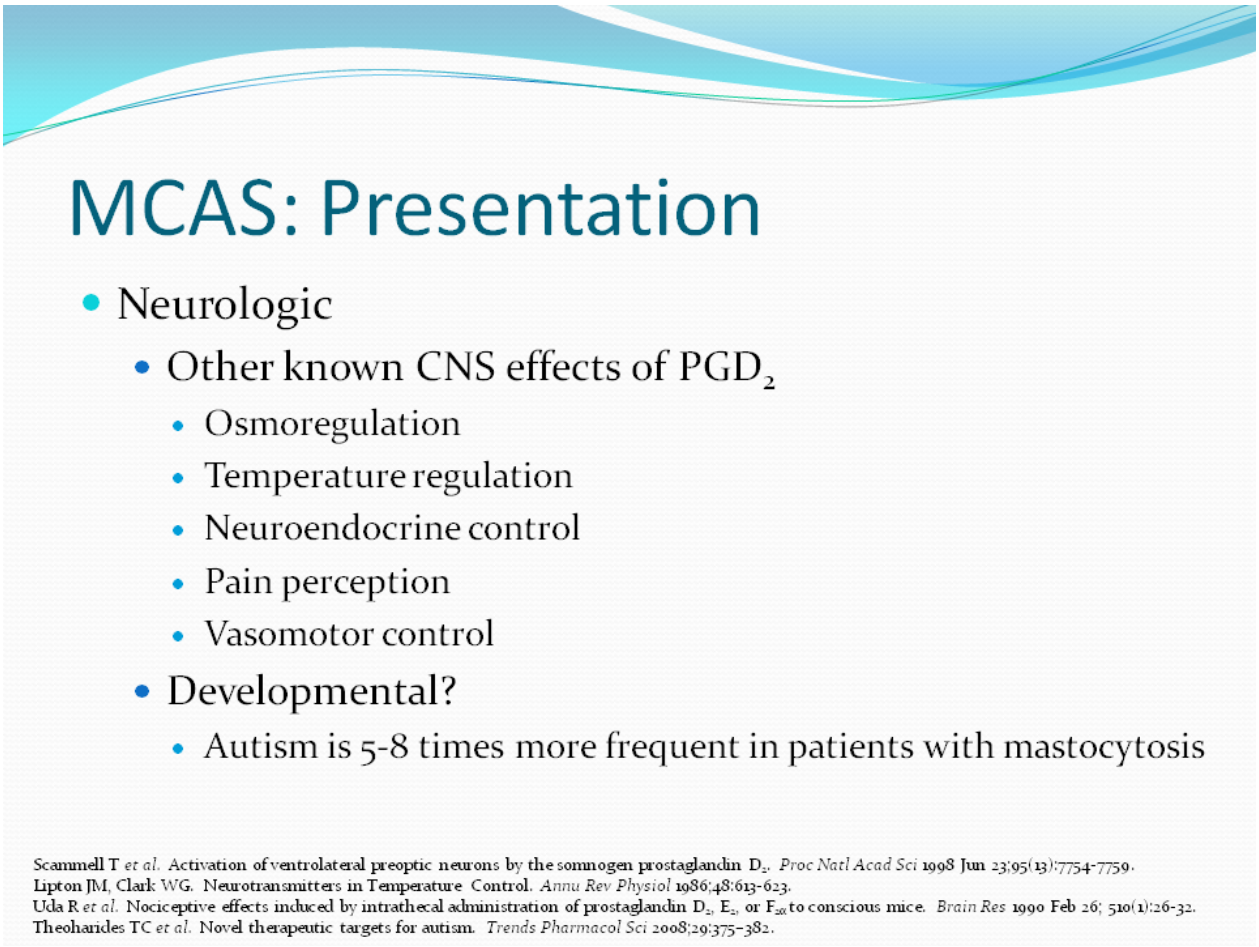
Neurologic issues, too, are all over the map, including headaches, especially migraines. I have now lost count of the number of these patients who've come to me over the last few years with refractory migraine headaches, and simple antihistamines were all it took to eliminate the headaches. To be sure, this approach has not worked for all of my MCAS patients with migraine headaches, but it has helped a not insignificant number of them. Again, it just emphasizes the importance of getting the right diagnosis. Syncope and dizziness are common complaints, and many of my patients labeled with POTS have also been labeled with dysautonomia. There can be actual demyelination. Many MCAS patients have migratory sensory neuropathies (tingling and numbness) that migrates around, but it also waxes and wanes, and if you follow it over time it's clear it's not a true demyelination going on. There's growing evidence implicating mast cell disease in multiple sclerosis and amyotrophic lateral sclerosis, but we haven't found the "smoking gun" yet to definitively attribute those diseases to mast cell disease.

[Slide 70: MCAS: Presentation.]



Sleep issues are quite common. It's usually insomnia, but I've now seen virtually every type of sleep disturbance across my pool of MCAS patients. Certain mast cell mediators can cause interesting sleep disturbances. Weight gain can lead to obstructive sleep apnea which can produce a whole range of its own symptoms. Sometimes, if you just treat the sleep apnea, you can get significant symptomatic improvement. Conversely, I've also seen a number of MCAS patients who are very slim but clearly have obstructive sleep apnea. I'm beginning to wonder if there's some mediator imbalance that affects pharyngeal muscle tone during sleep so that even if you're not obese, you might still be able to develop obstructive sleep apnea.

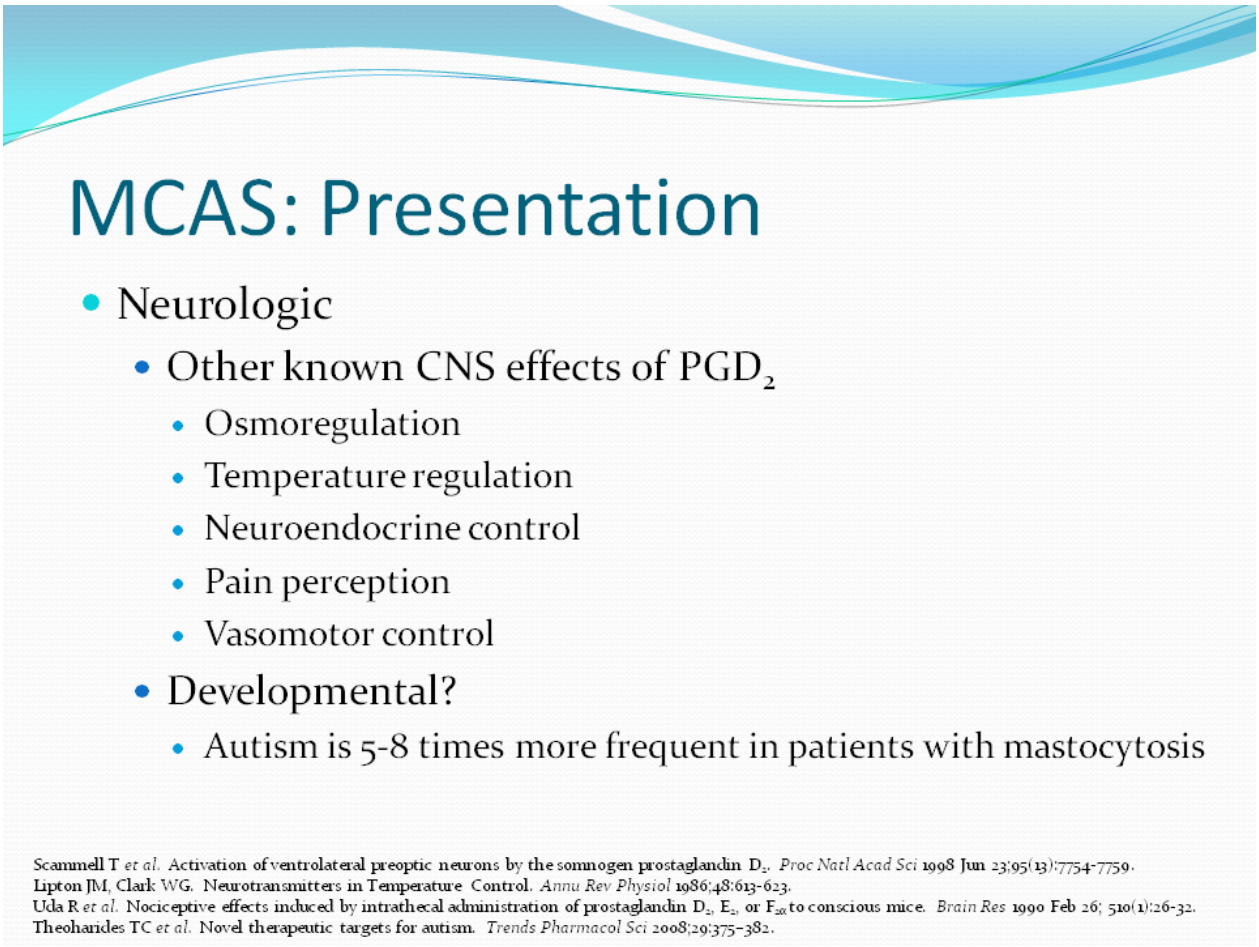
[Slide 71: MCAS Presentation]



The disease clearly impacts a number of hormonal issues helping you to better understand the constitutional symptoms.

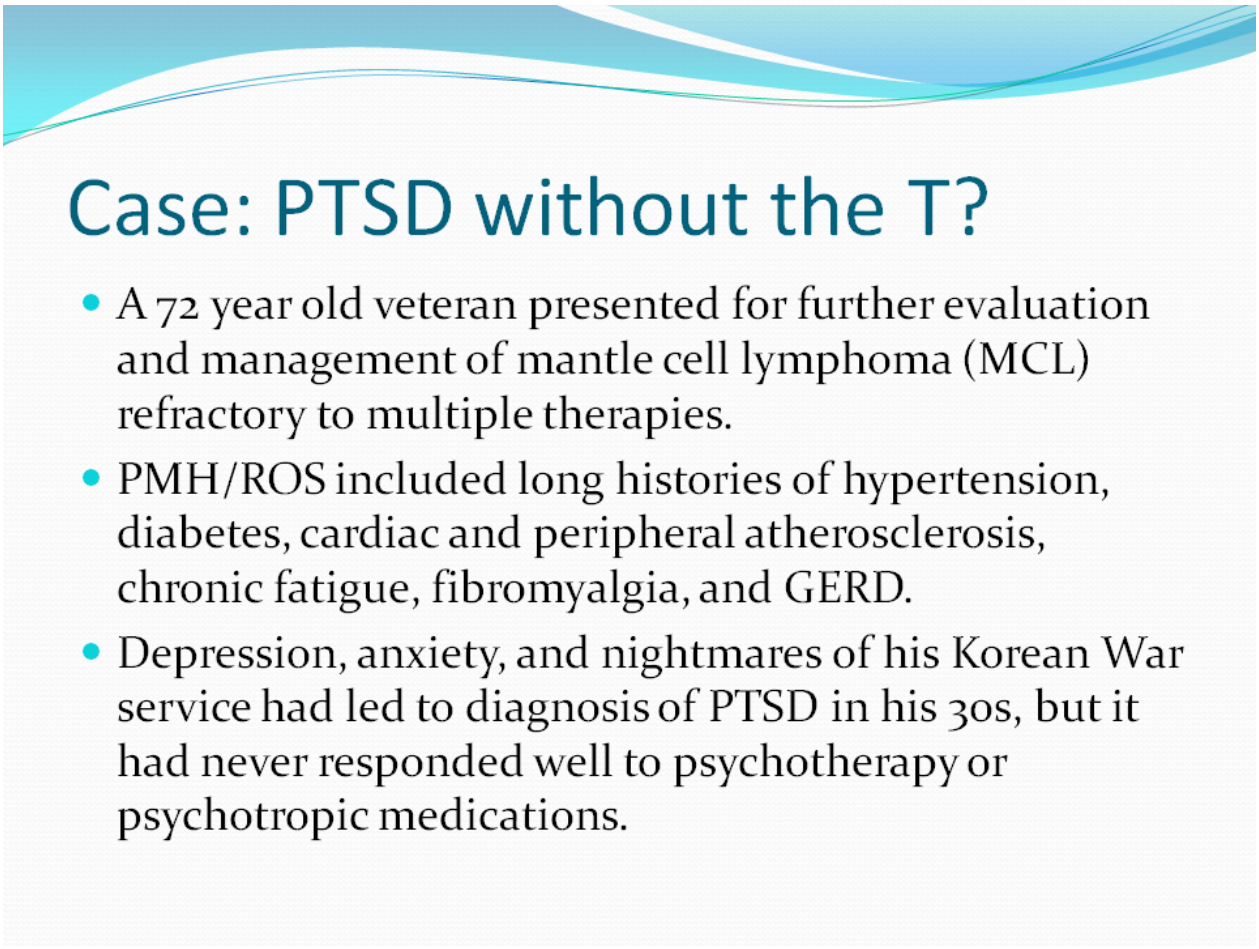
Furthermore, we now know that autism is up to 10 times more frequent in patients with mastocytosis, making me wonder if chronic expression of certain specific aberrant mediator patterns could impact neural development so as to lead to autism. We don't know. Right now this is just a statistical association between autism and mast cell disease, but, given the known biology of the mast cell, it's a biologically plausible theory which also could explain other curious aspects of the autism such as the anecdotal reports of the condition developing relatively soon after acute reactions to routine childhood vaccinations.

[Slide 72: MCAS: Presentation.]



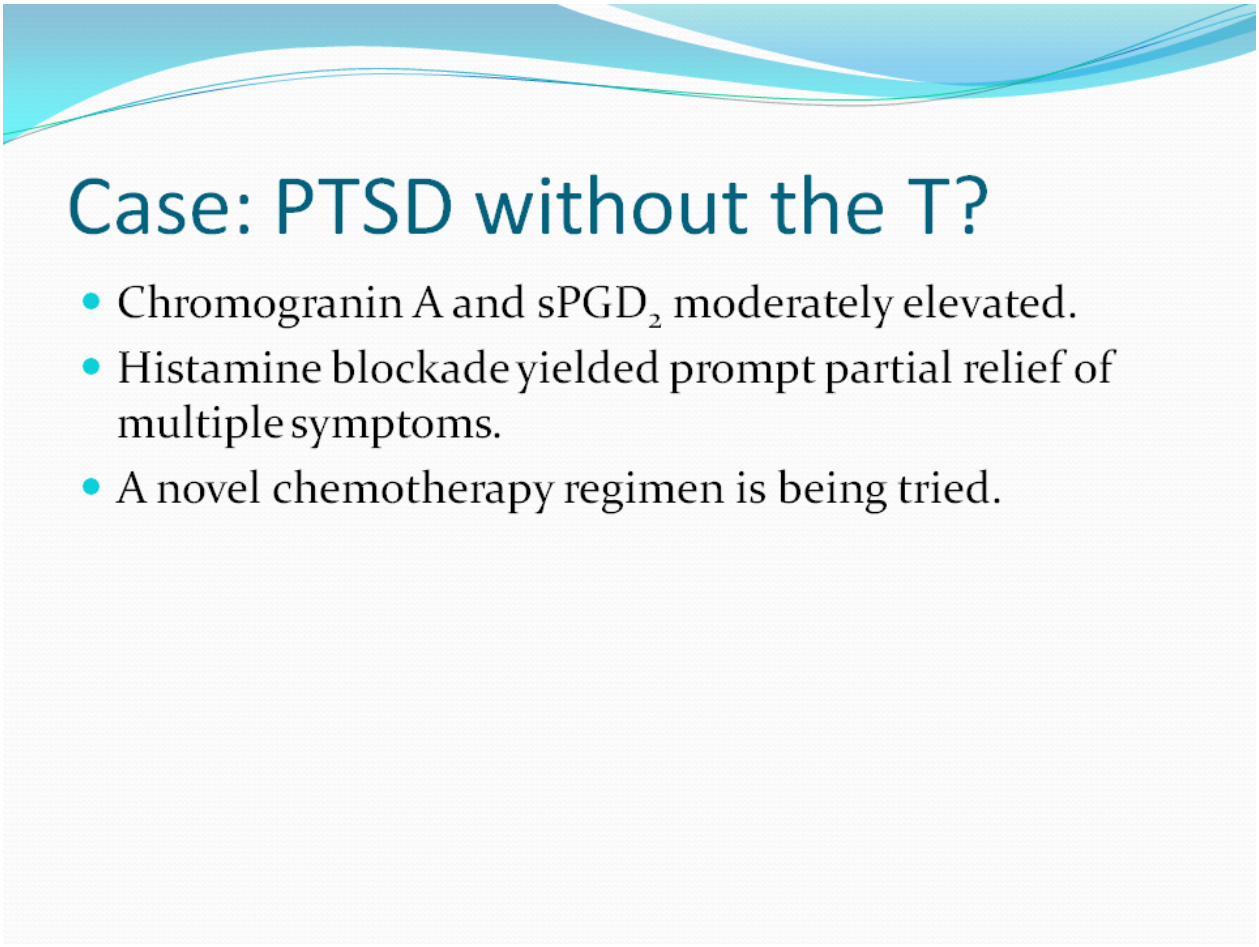
The psychiatric issues in MCAS are just as broad-ranging as the symptoms found in every other system. There is no major DSM Axis 1 disorder that has not been diagnosed in a patient with mast cell disease. Maybe Axis 2 disorders tie into this as well, but we don't know.

[Slides 73-75: Case: PTSD without the T?]



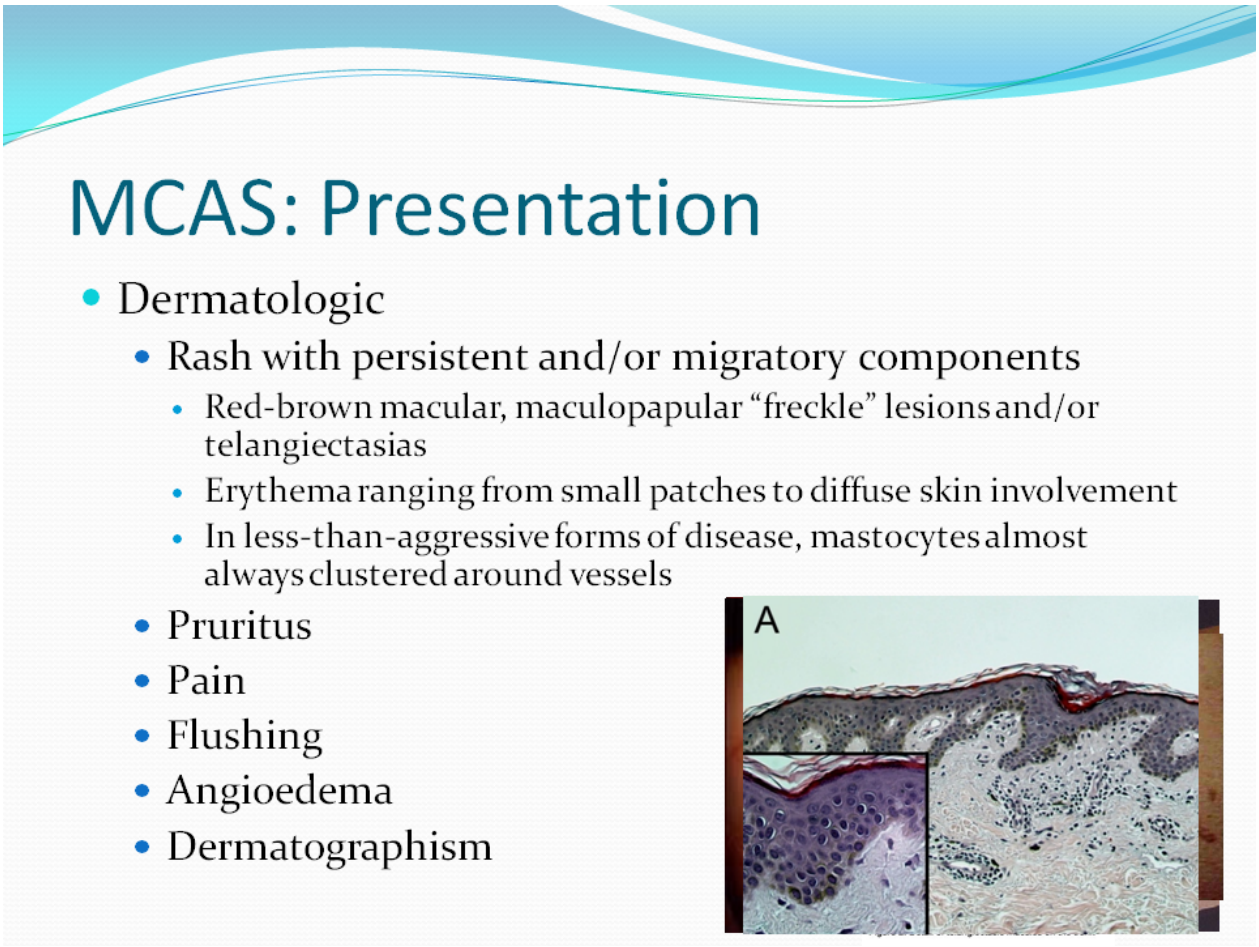
Case: PTSD without the T?

- On further evaluation:
  - His lymphoma did not bear classic MCL molecular markers and histologically was not classic for MCL but was reported as "most consistent" with MCL.
  - He had never experienced battle. Before deployment to the front, he experienced two episodes of spontaneous, unprovoked syncope the first two days after arriving in Seoul (each time while walking down the street with others from his unit) and was discharged.



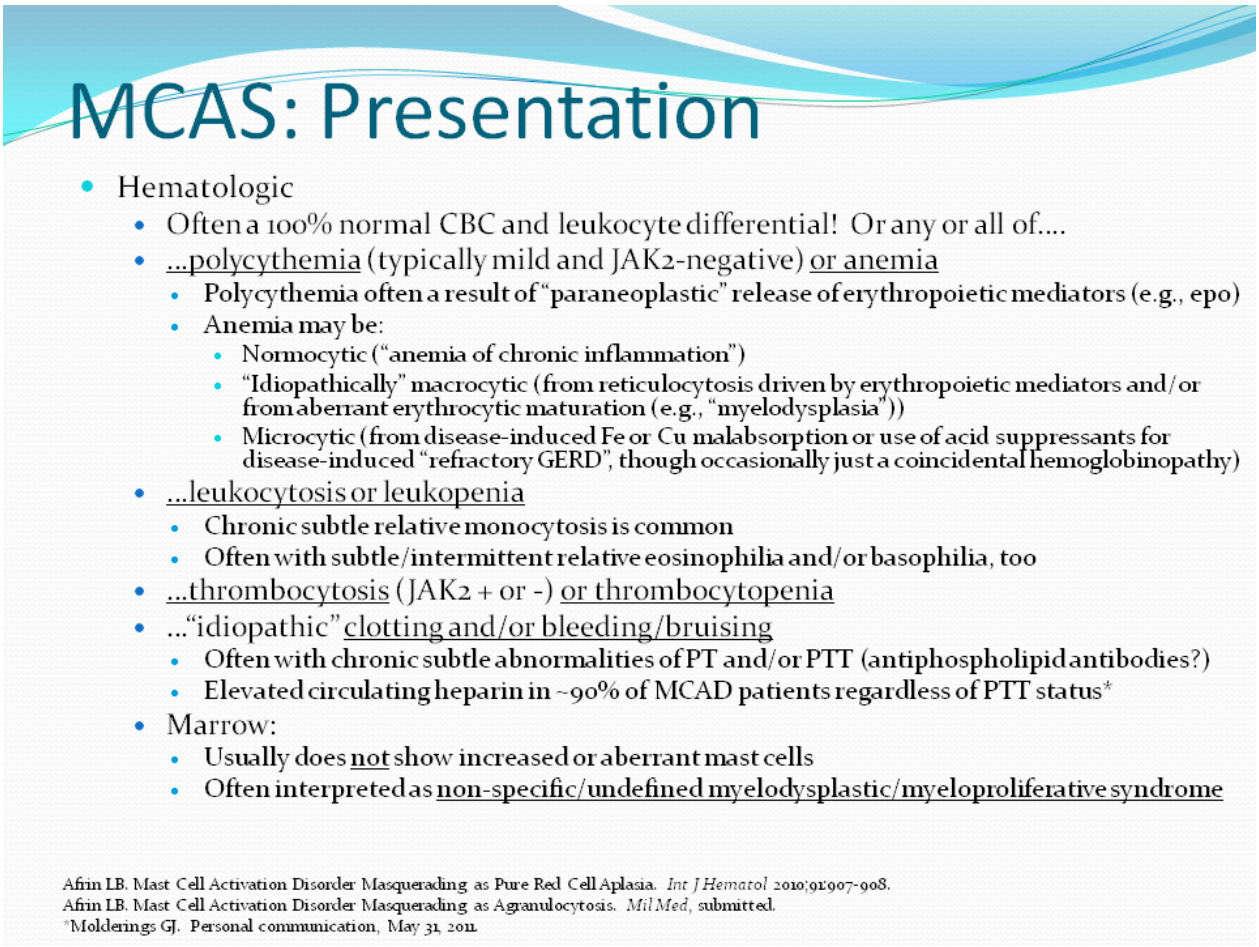
A 72 year old veteran presented for further evaluation and management of mantle cell lymphoma refractory to multiple therapies. We took a detailed history and found a lot of problems that had been going on for decades which could not possibly be attributed to his lymphoma. Most interestingly, he also had PTSD (post traumatic stress disorder) from his Korean War service. He'd had this diagnosis since his 30's, but he had never responded to any therapy for it. On first evaluation for lymphoma, it didn't look like the classic picture of lymphoma, and when we went into the history of PTSD, I asked him to tell me about his war experience. He said he didn't have any. He went through basic training, was deployed to Korea, landed in Seoul and had 2 days before being shipped to the front. He was walking down the street and passed out on two different occasions. The Army discharged him because of that. Ten years later the battle nightmares began. He was diagnosed with PTSD (again underscoring the importance of an accurate history), but it was never successfully treated and his symptoms persisted despite multiple medication trials and efforts at various types of talk therapy. He turned out to have an elevated serum chromogranin A. He does have lymphoma, but closer examination of the pathology found it actually wasn't mantle cell lymphoma and now the pathologist has decided he can only call it a non-classifiable lymphoma.

[Slide 76: MCAS: Presentation.]



Dermatologic issues, too, are "all over the map." Fundamentally, this disease seems as if it can make your skin do anything. Dermatographism is quite frequent, and pruritis can be very troublesome.

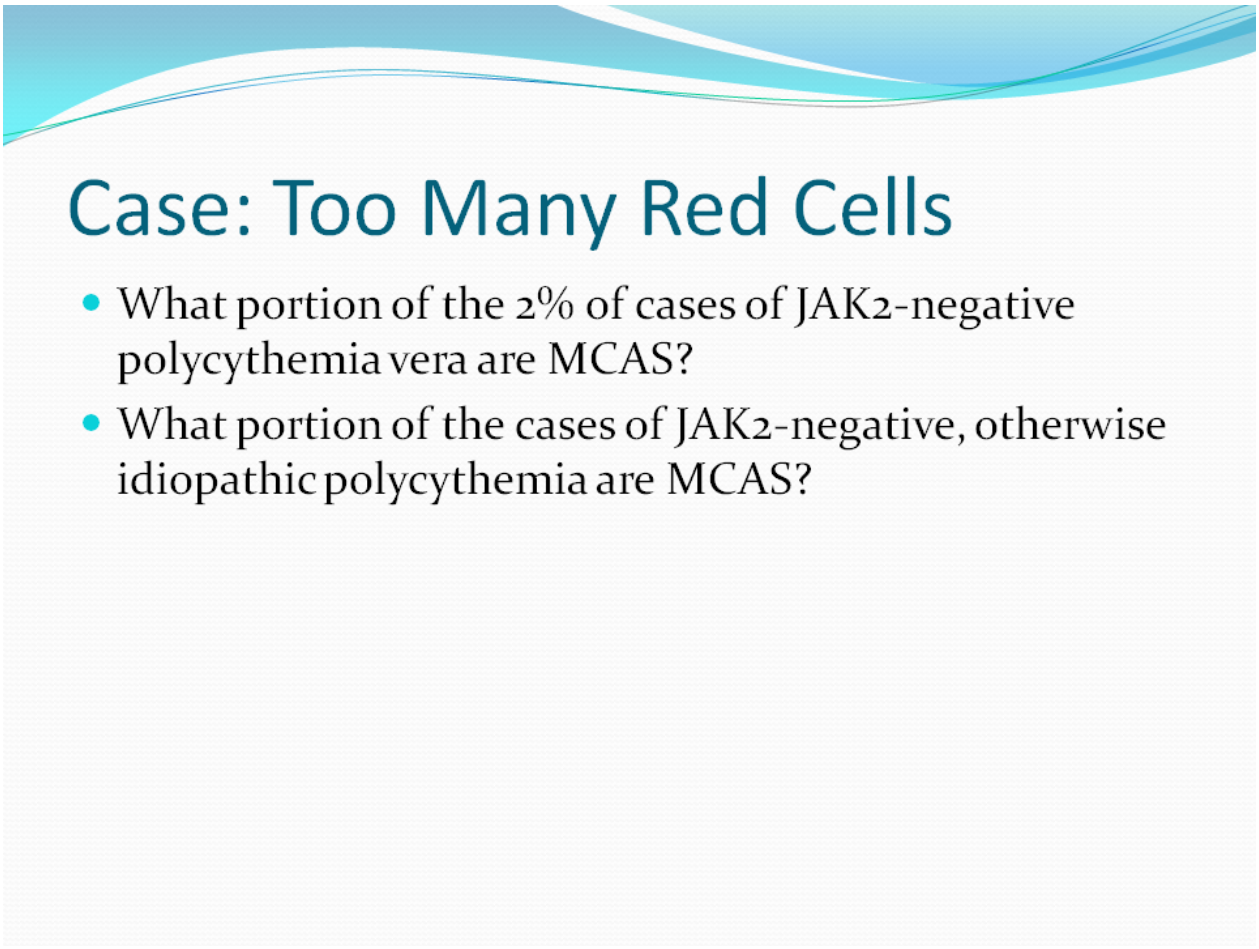
[Slide 77: MCAS: Presentation.]

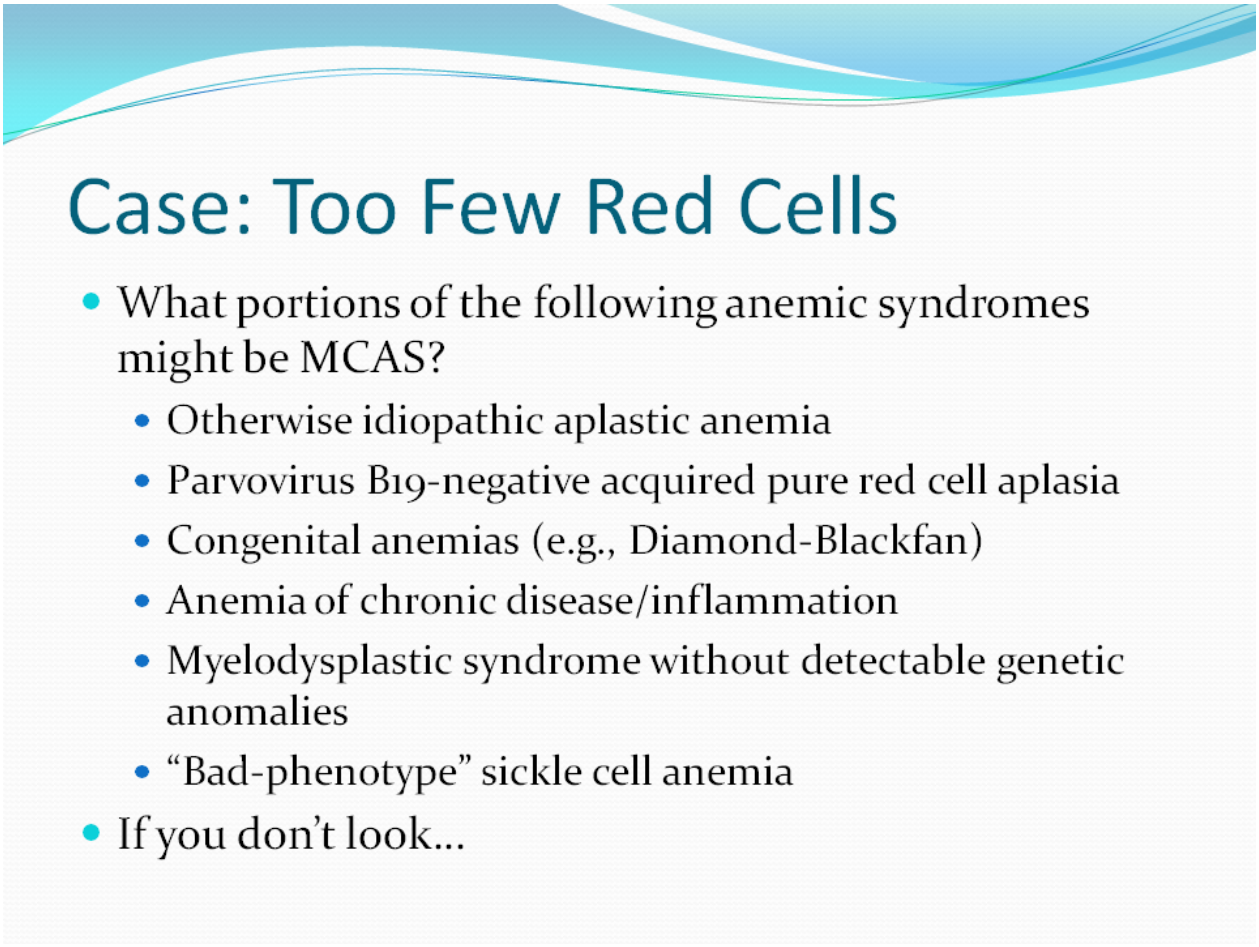


The most common hematologic presentation of this hematologic disease is a 100% normal CBC, which in my experience seems to confound most hematologists given that mast cell disease is classified as a hematologic disease. It certainly confounded me, too, at least initially. However, it's clear that mast cell disease can present with any or all of the hematologic problems listed on this slide including polycythemia or anemia (i.e., too many or too few red cells, which can be normal, enlarged, or reduced in size for various reasons), too many or too few white cells, too many or too few platelets, and/or too much or too little clotting. The most common abnormal presentation in peripheral blood in these patients is a chronic subtle relative monocytosis (not an absolute monocytosis). If you look at the white cell differential, where the upper limit of normal for monocytes is about 10%, you'll see modest elevations – a few percentage points at most – above that limit. If you look at that long list of mediators these cells elaborate, monocyte growth factor is on the list. I don't know that that's the growth factor that's causing the increase in monocytes, but clearly there are growth factors being elaborated by the disease that are capable of increasing monocytes.

Now with regard to your difficulty getting the PGD_2 testing, again, I got information just last week that you can find elevated circulating heparin in about 90% of these patients. So I don't know if the plasma heparin level is any easier for you to get than the PGD_2, but if so, that may be the test to go for. The upper limit of normal varies amongst laboratories but typically is 0.020 anti-Factor-Xa units/ml. Many of these patients will have elevated levels of heparin even if the partial thromboplastin time (PTT) is normal. In MCAS, the most common marrow pattern is completely normal findings on every test including histology, flow cytometry, cytogenetics, and mutation analysis by polymerase chain reaction. The most common abnormal pattern is a non-specific myelodysplastic/myeloproliferative syndrome, which is the pathologist's way of telling you something isn't quite right about the marrow, but they can't figure out what the problem specifically is. Often, once the pathology report has mentioned that term of myelodysplasia, the patient gets diagnosed with "cytogenetically normal myelodysplastic syndrome," the hematologist never thinks about mast cell disease, and the patient winds up getting treated for myelodysplastic syndrome with no good results because that's the wrong diagnosis and the wrong treatment.

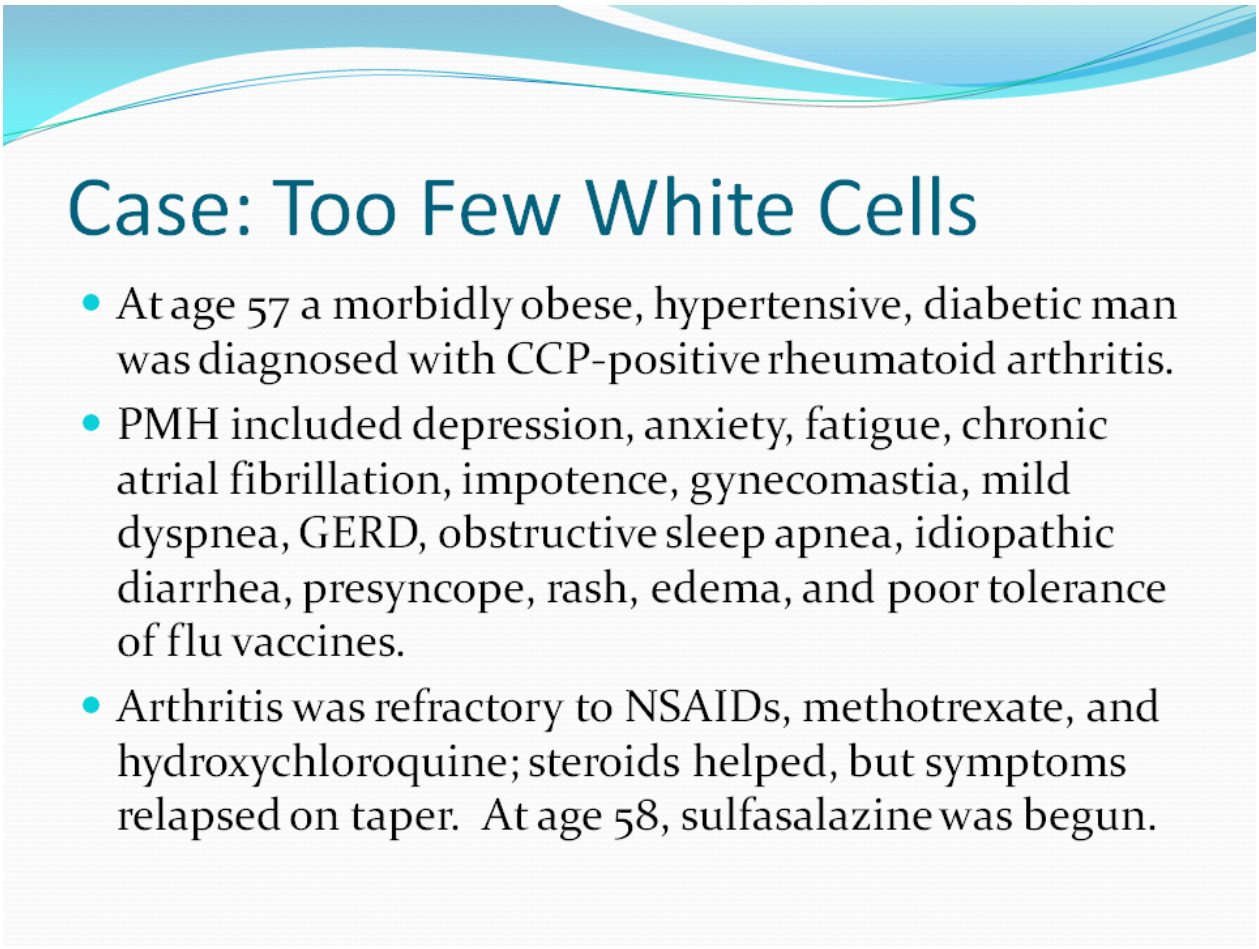
[Slides 78-79: Case: Too Many or Too Few Red Cells]





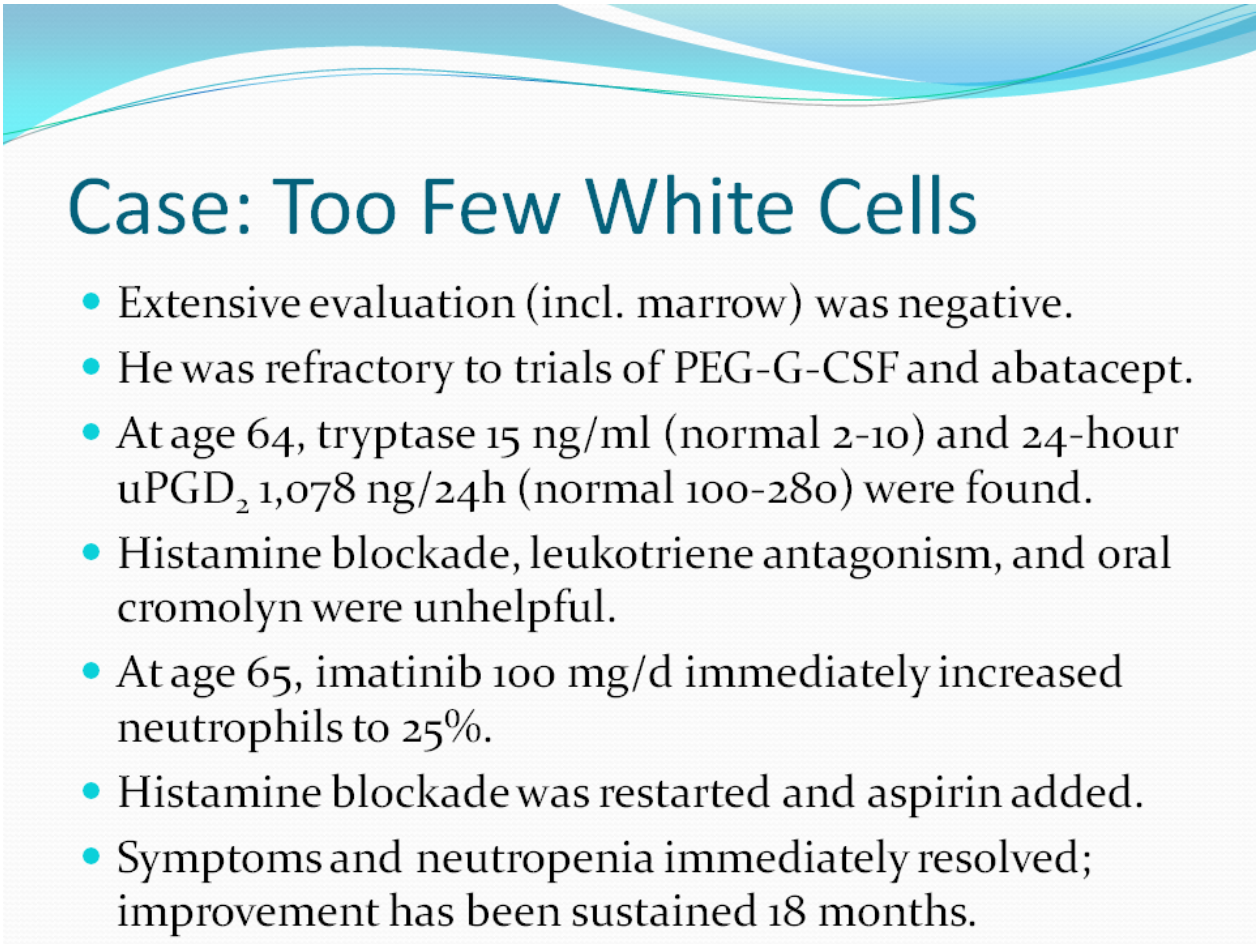
A number of polycythemias or anemias which presently are idiopathic but which seem to well fit MCAS (e.g., anemia of chronic disease/inflammation, poorly behaving sickle cell anemia) might in fact be MCAS, or at least MCAS as an acquired co-morbidity to the inborn disease.

[Slides 80-82: Case: Too Few White Cells]



Case: Too Few White Cells

- One month later sulfasalazine was stopped due to non-response. The plummeting of the previously normal absolute neutrophil count to zero was missed.
- Repeated "URIs" ensued, initially mild (permitting outpatient treatment) but worsening over time. No infectant was ever identified. ANC remained zero and remained overlooked.
- At age 61 he was referred for evaluation of newly recognized agranulocytosis.



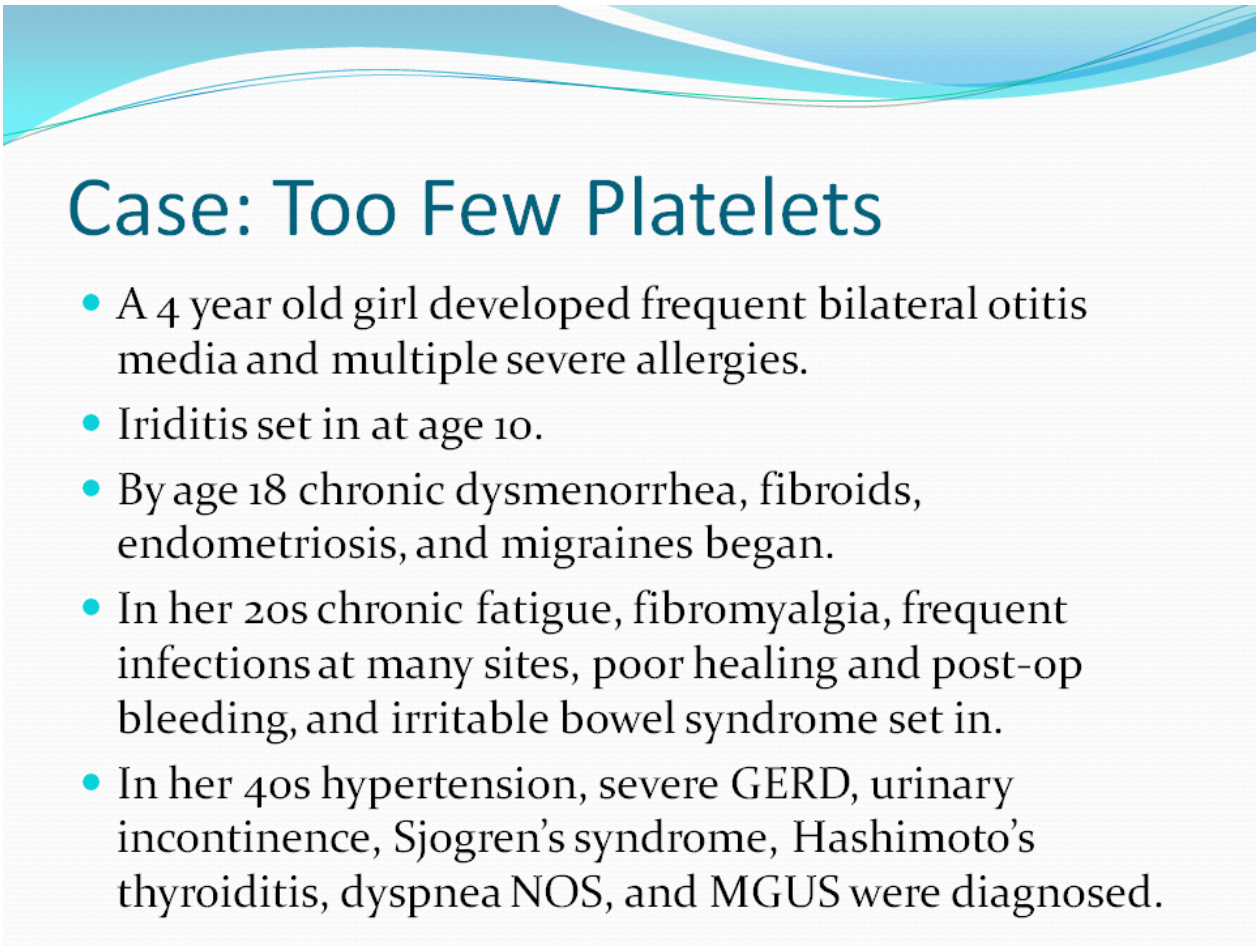
I've shown you a case with too many red cells, and I've shown you a case with too few red cells. Here now is a white cell issue. At age 57 a morbidly obese hypertensive diabetic was diagnosed with rheumatoid of arthritis. He had many problems, but the rheumatologist could focus only on the arthritis, which proved to be refractory to multiple drugs. Steroids helped only a little bit. Finally, he was given sulfasalazine, which was stopped one month later because it wasn't helping his arthritis. His primary care physician failed to notice at that time, in spite of having ordered a CBC, that the absolute neutrophil count (ANC) had dropped to zero. Now, agranulocytosis is a recognized potential complication of sulfasalazine, but when you stop the drug, the ANC is supposed to rebound. That did not happen here. Repeated upper respiratory "infections" ensued even though no infectant could ever be found. At age 61, three years later, finally the ANC of zero was seen despite there having been many interim CBCs in which the agranulocytosis was never recognized. He was referred to me and underwent an extensive evaluation, including a marrow exam, all of which was unrevealing. Finally, we had an opportunity to check for mast cell disease. Tryptase was only modestly elevated and did not meet WHO criteria. However, he had the third highest level of PGD_2 I've ever seen. I tried inexpensive interventions, but none of them worked. I then tried him on low dose imatinib, and immediately the ANC rebounded from 0 (where it had been for

6 years at that point). He was beginning to have serious infections and unhealed wounds and lots of surgery to heal them, but imatinib got the ANC up to 25%, and then I decided to try adding aspirin along with some protective antihistamines. I had not done aspirin initially because he was also on warfarin, but then we decided to at least briefly try it. He tolerated it well with no apparent complications, and his ANC immediately reverted to normal with just a modest 325 mg aspirin dose added to imatinib.

Shelley: Earlier you mentioned that when you are KIT-positive that imatinib sometimes can help. Are these cases KIT-positive?

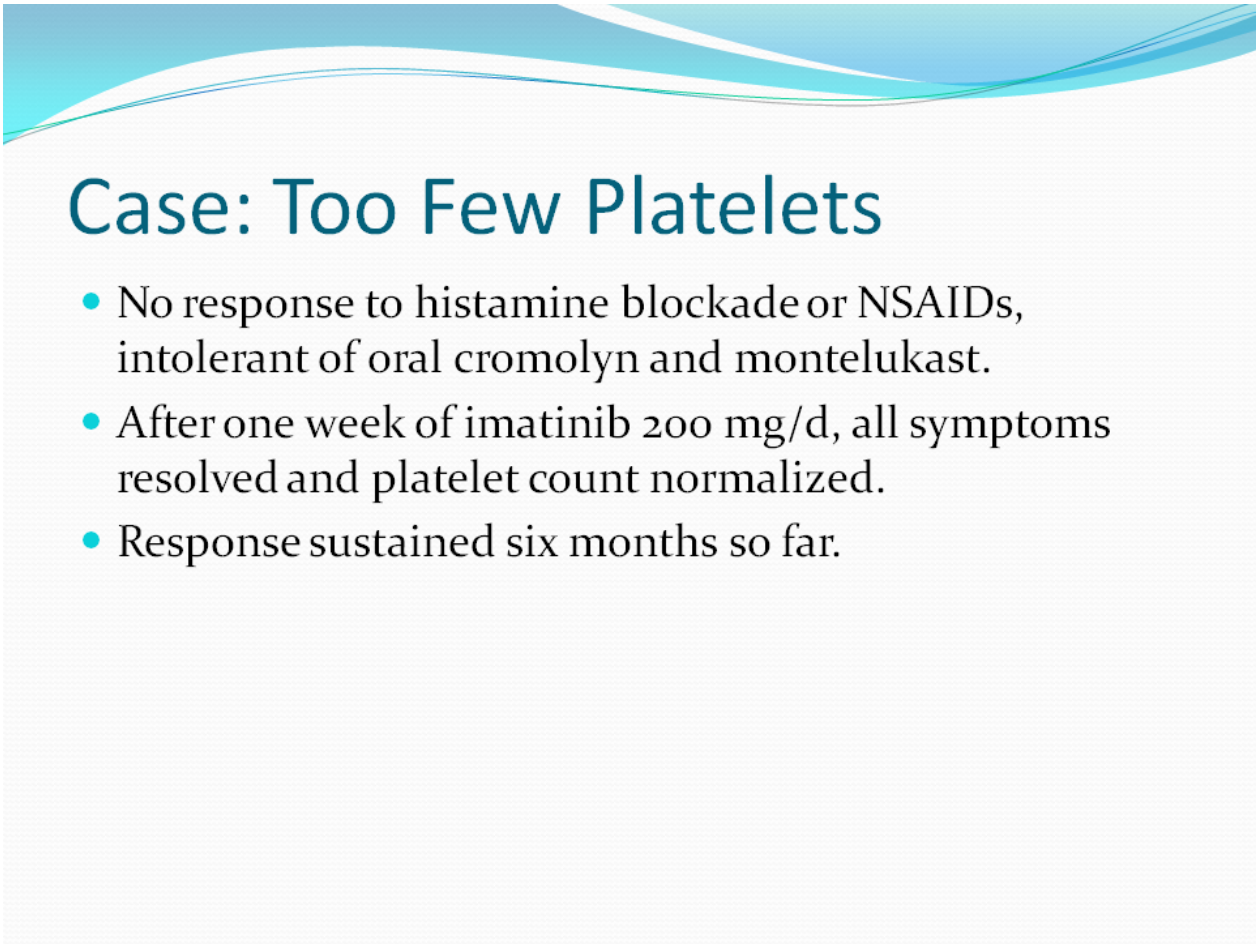
Dr. Afrin: We don't know in him because we couldn't do the GI biopsies safely due to his being on warfarin. I suspect the reason imatinib can work in some patients with the D816V mutation is that most of these patients have multiple mutations. We know imatinib can stabilize some of the other mutations, i.e., it doesn't focus just on the D816V mutation. We don't exactly know the molecular mechanism yet of how it stabilizes the other mutations or which ones. The fundamental issue with mutations is that although KIT is ordinarily quiescent until it gets activated by stem cell factor, these mutations lead to constitutive activation of KIT. Once KIT is always on, you've got to find a way to stabilize it.

[Slides 84-86: Case: Too few platelets.]



Case: Too Few Platelets

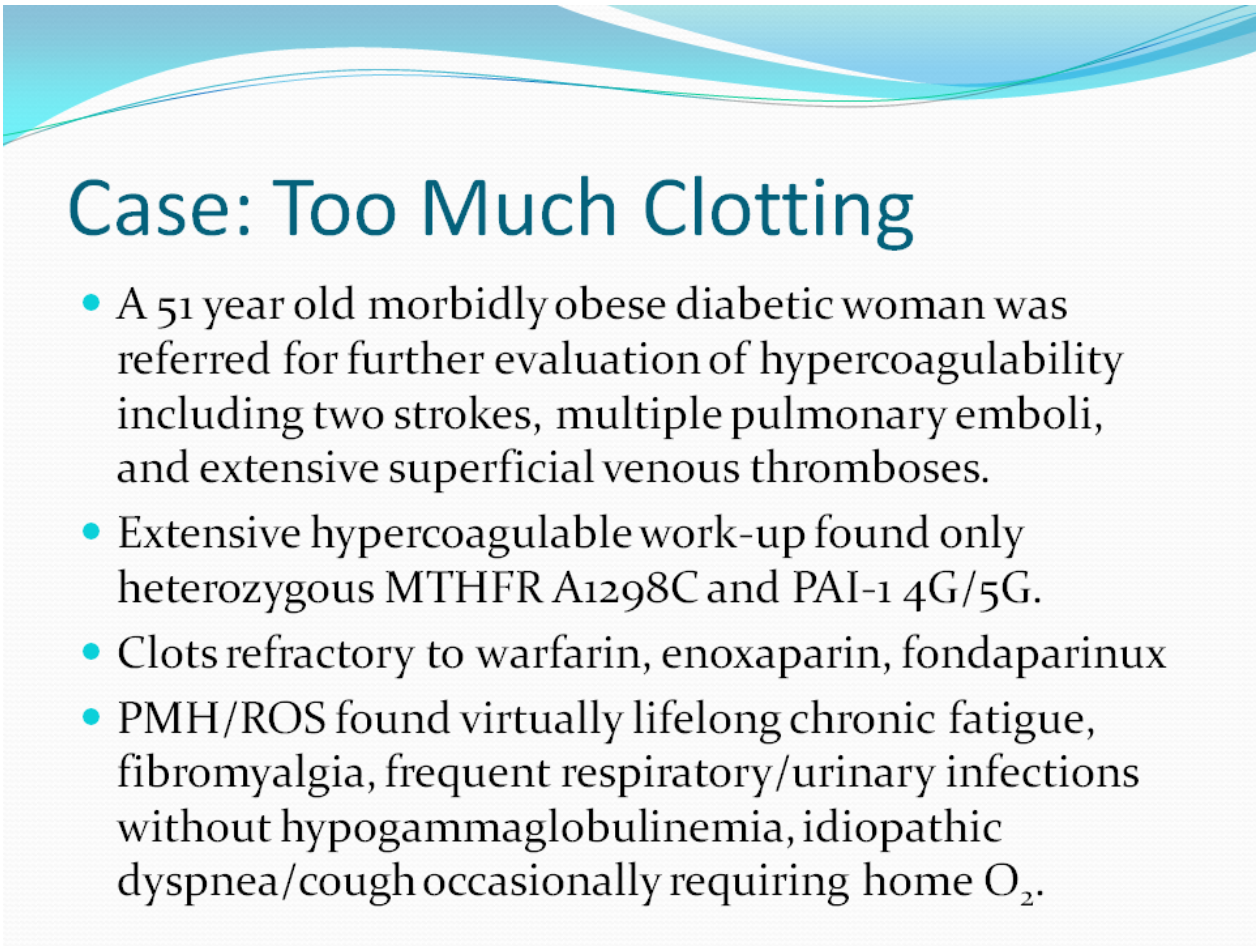
- Referred at age 50 for thrombocytopenia; work-up consistent with ITP.
- ROS positive for fevers, chills, sweats, headaches, sinusitis, pruritus, mouth and throat soreness, CPAP-refractory obstructive sleep apnea (non-obese!), palpitations, malaise, sensory neuropathies, edema, insomnia, depression, dyspareunia, cognitive dysfunction, frequent presyncope.
  - Was this really Sjogren's?
- Tryptase elevated 2.5-fold; duodenal mast cells ↑'ed

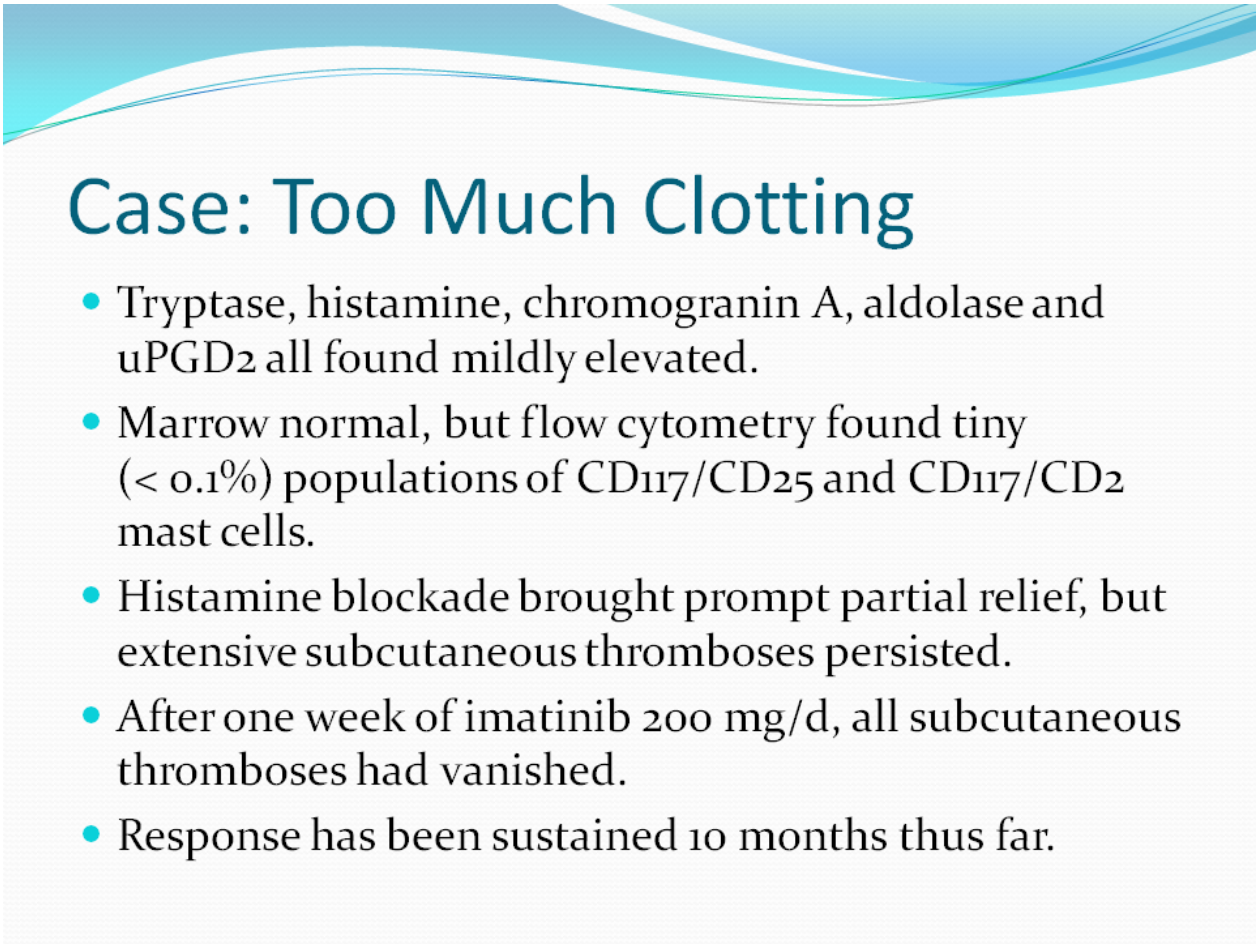


I'm skipping over cases because we're running late.

This basically was a case of ITP. She had had multiple problems throughout her life going back to childhood and was eventually referred for consideration of immune thrombocytopenic purpura (low platelets) evolving due to Sjogren's Syndrome. Her Sjogren's Syndrome was not really behaving like Sjogren's Syndrome is supposed to behave, but we also found her tryptase was elevated, mast cells were increased in the duodenum, and eventually she turned out to do well – symptoms and platelet count – on imatinib.

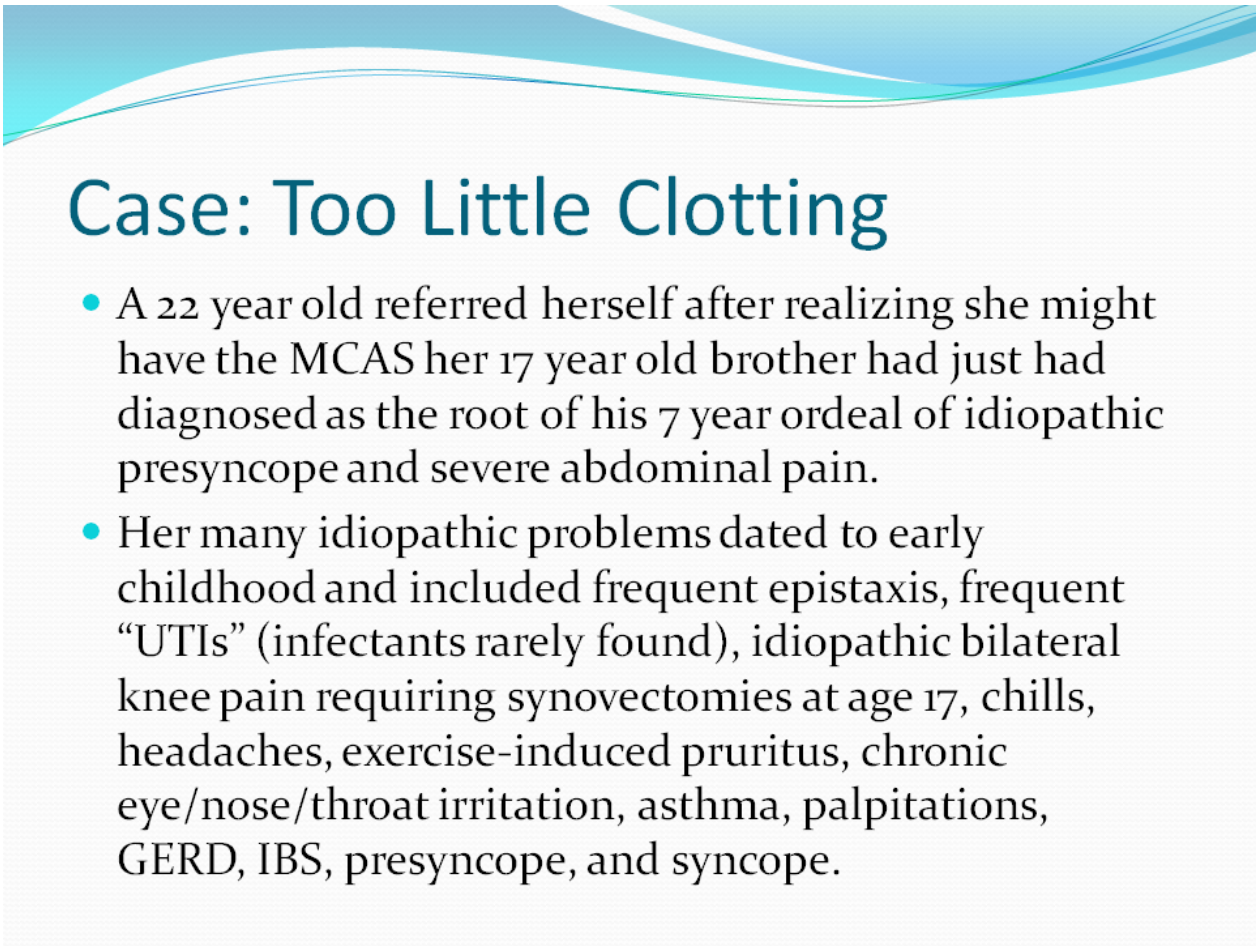
[Slides 87-88: Case: Too Much Clotting.]

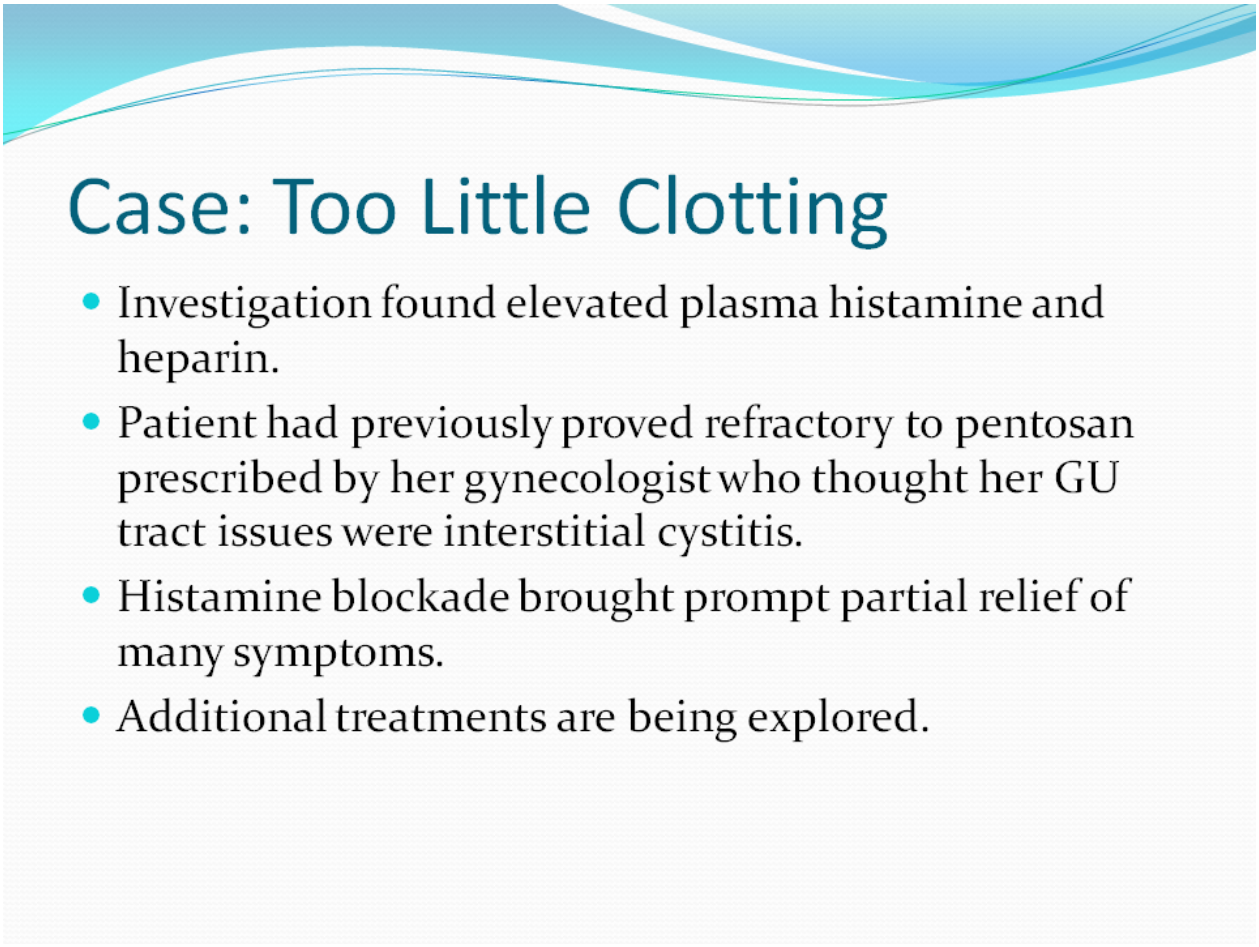




A 51 year old morbidly obese diabetic woman was referred for further evaluation of hypercoagulability including lots of clots. Her exam was really impressive. You could feel multiple superficial venous clots all over her skin. Extensive workup found just a couple of modest abnormalities that couldn't possibly account for such severe clotting. She was refractory to multiple agents. She turned out to have multiple positive markers for MCAS, and she was one of the few MCAS patients who actually showed an abnormal population of mast cells in her marrow, though, as usual in those few MCAS patients who have positive marrow findings, this was detectable only on flow cytometry. Histamine blockade brought prompt partial relief of some symptoms, but the thromboses persisted. Then I put her on low-dose imatinib, and she came back a month later with complete resolution of all of the superficial thrombosis. Due to financial issues, she stopped imatinib, and all of her prior problems came back. She then was able to resume imatinib, and all of her problems went away again.

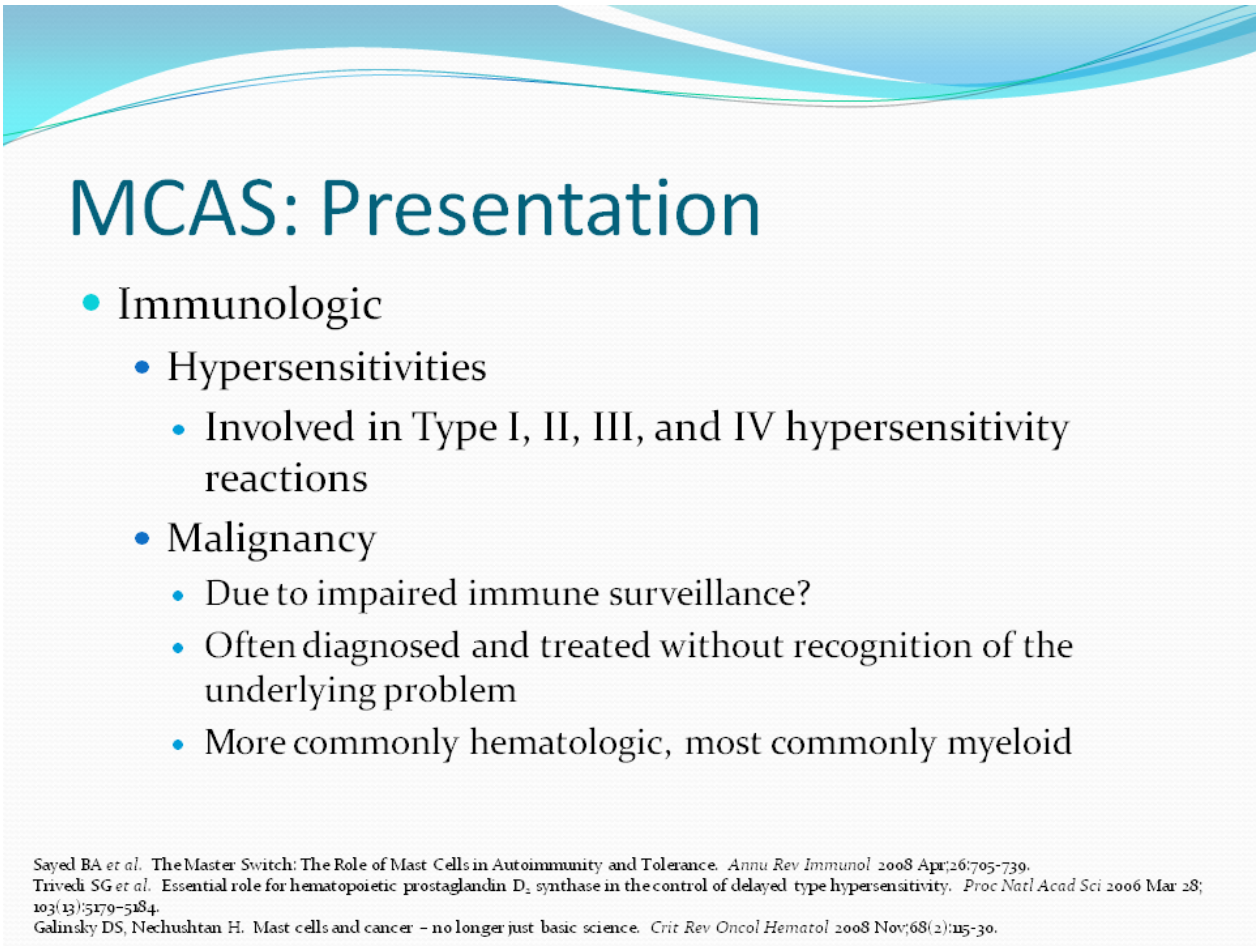
[Slides 89-90: Case: Too Little Clotting.]

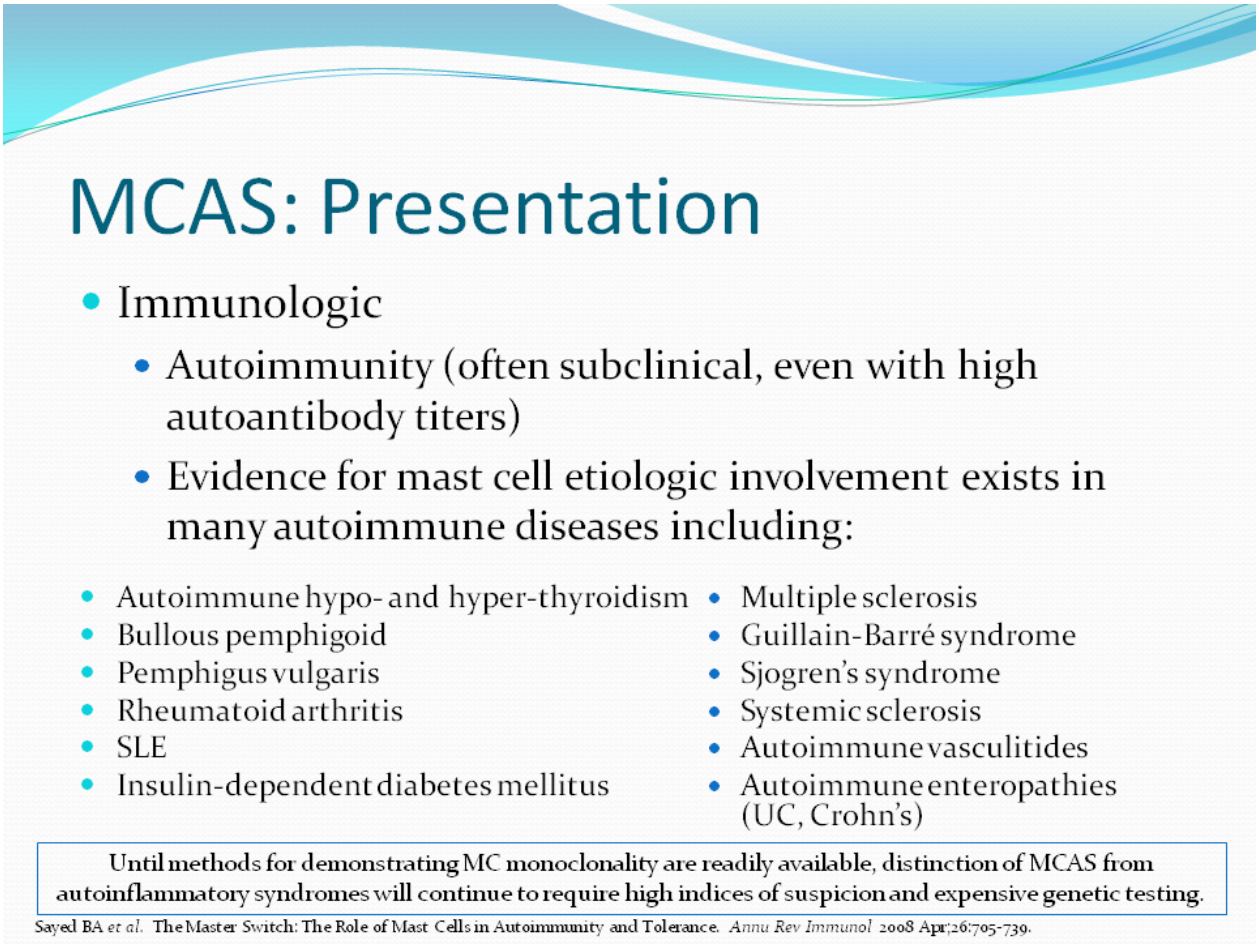




A 22 year old woman referred herself after realizing she might have MCAS since her 17 year old brother had just been diagnosed with MCAS as the root of his seven year ordeal. Her many problems included frequent epistaxis which had undergone extensive evaluation, and her physicians (including ENT physicians) could never find a cause for it. She also had many other problems. She was found to have an elevated plasma histamine and elevated heparin, and her intractable pelvic pain turned out to be an interstitial cystitis. She has responded somewhat to histamine blockade.

[Slides 91-95: MCAS: Presentation.]




MCAS: Presentation
Immunologic
Autoimmunity (often subclinical, even with high autoantibody titers)
Evidence for mast cell etiologic involvement exists in many autoimmune diseases including:
Autoimmune hypo- and hyper-thyroidism
Bullous pemphigoid
Pemphigus vulgaris
Rheumatoid arthritis
SLE
Insulin-dependent diabetes mellitus
Multiple sclerosis
Guillain-Barré syndrome
Sjogren's syndrome
Systemic sclerosis
Autoimmune vasculitides
Autoimmune enteropathies (UC, Crohn's)
Until methods for demonstrating MC monoclonality are readily available, distinction of MCAS from autoinflammatory syndromes will continue to require high indices of suspicion and expensive genetic testing.
Sayed BA et al. The Master Switch: The Role of Mast Cells in Autoimmunity and Tolerance. Annu Rev Immunol 2008 Apr;26:705-739.

MCAS: Presentation

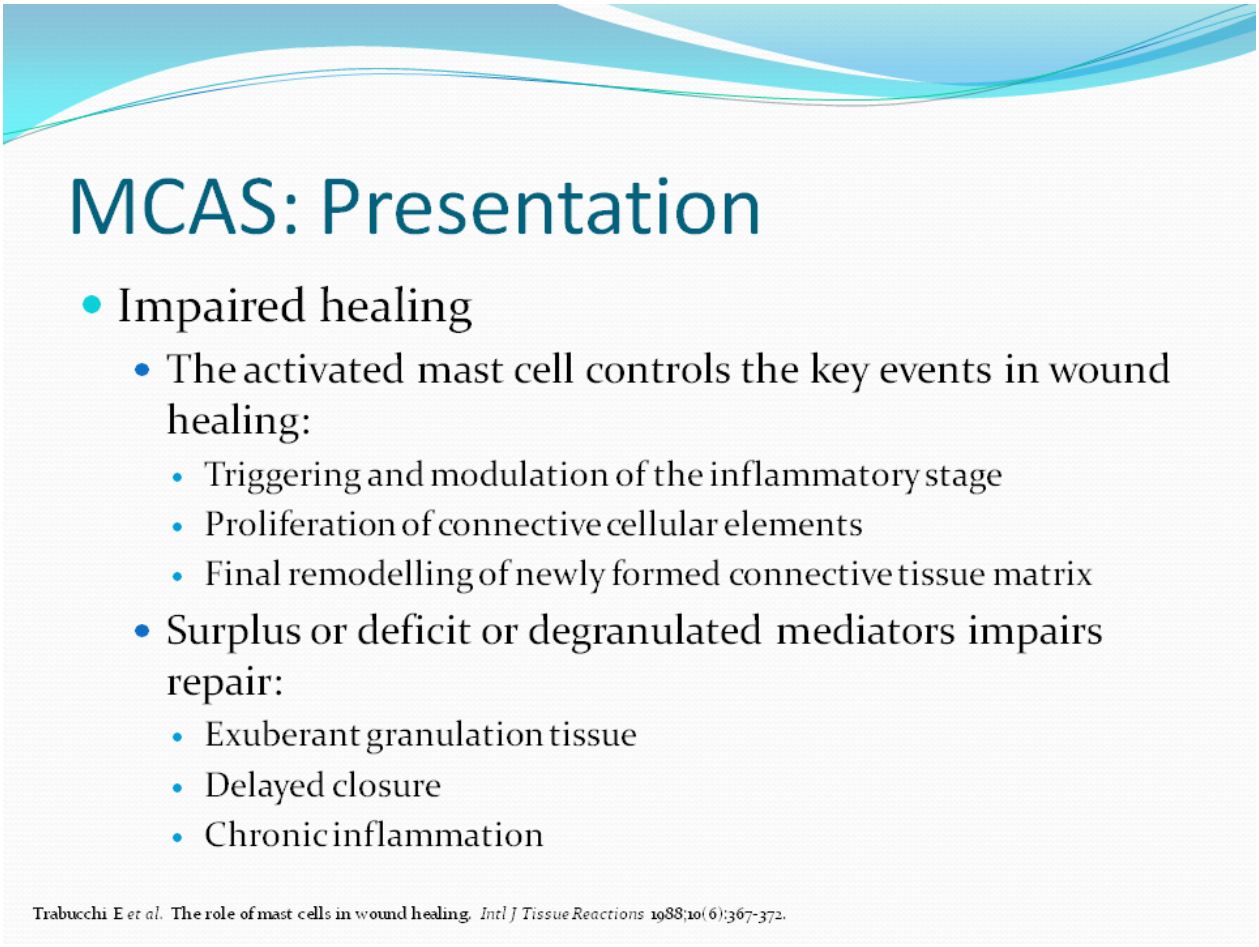
- Immunologic
  - Autoimmunity
    - Mast cells influence initiation and effector phases of autoimmune diseases via many mechanisms including:
      - Promoting dendritic cell maturation and migration to secondary lymphoid organs
      - Directing T cell differentiation
      - Orchestrating the migration of T cells and other immune cells to the sites of tissue inflammation
    - Variable effects of mast cells are related to:
      - The activating stimulus
      - Tissue site
      - Proximal target cells
      - Genetically determined variability in mediator production

Sayed BA *et al.* The Master Switch: The Role of Mast Cells in Autoimmunity and Tolerance. *Annu Rev Immunol* 2008 Apr;26:705-739.

MCAS: Presentation

- Infectious
  - Mast cells express TLR1, TLR2, TLR3, TLR4, TLR7, and TLR9
    - Important in response to bacteria, viruses, parasites
  - In addition to proinflammatory effects, mast cells have suppressive effects on some immune responses
  - Patients often have increased troubles with infection
    - More frequent infection than they previously experienced
      - Common and uncommon sites
      - Common and uncommon organisms
    - More prolonged infectious episodes even in spite of known correct antibiotic therapy

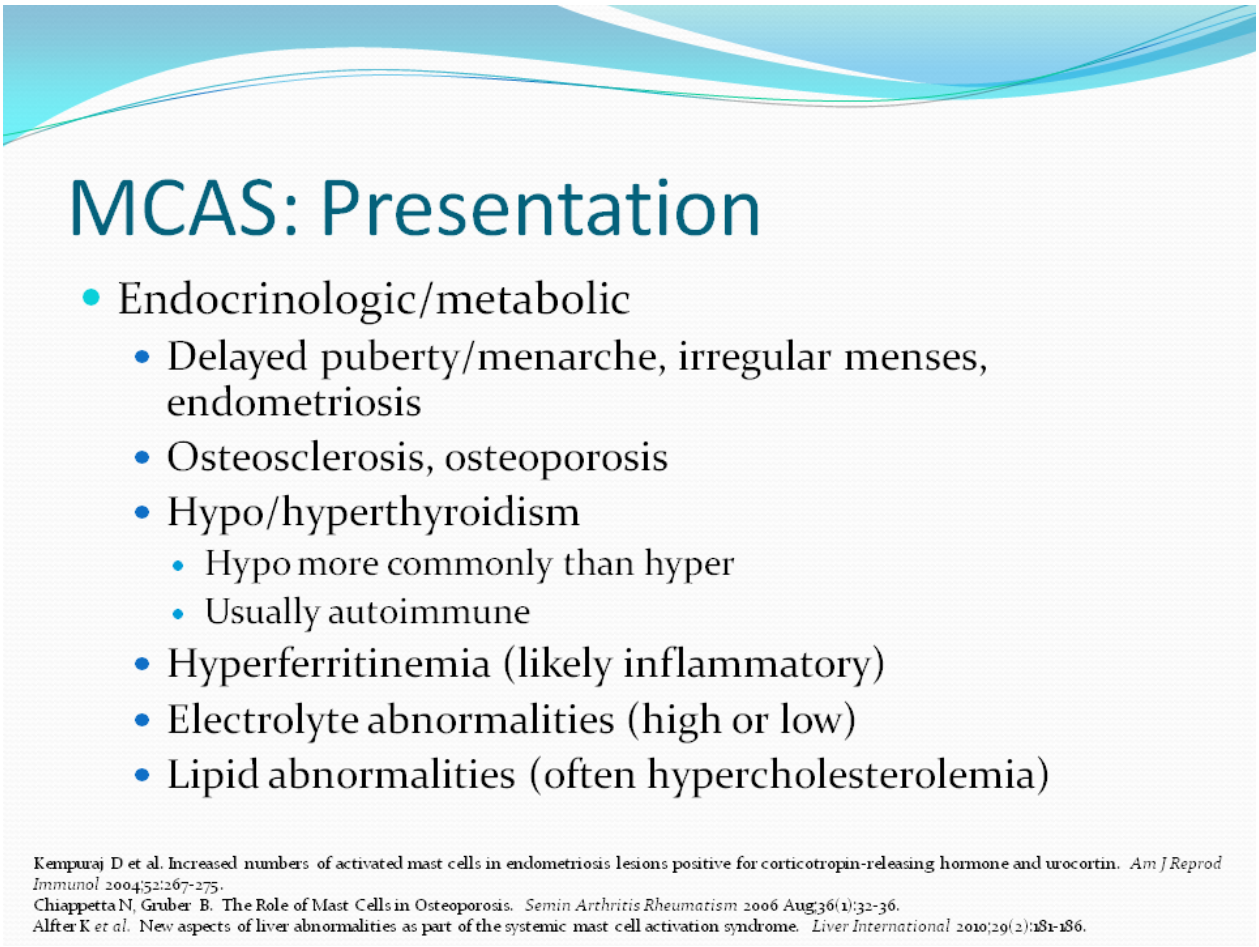
Sayed BA *et al.* The Master Switch: The Role of Mast Cells in Autoimmunity and Tolerance. *Annu Rev Immunol* 2008 Apr;26:705-739.
Ryan JJ, Fernando JF. Mast Cell Modulation of the Immune Response. *Curr Allergy Asthma Reports* 2009;9:353–359.



Immunologic issues are all over the map, too.

With mast cell diseases, the risks of malignancy seem to be increased, likely due to impaired immune surveillance which comes about because of the impact of the mediator expression pattern on immune system function. The malignancies are more commonly hematologic, most commonly myeloid, and can be solid tumour. You also get auto-immunity problems across the board in MCAS patients, plus increased troubles with infections, both the common and uncommon sites and organisms, and they just take longer to resolve even with known correct antibiotics. MCAS patients also just don't heal normally, both from infections and from wounds. Mast cells are known to be critical to proper wound healing.

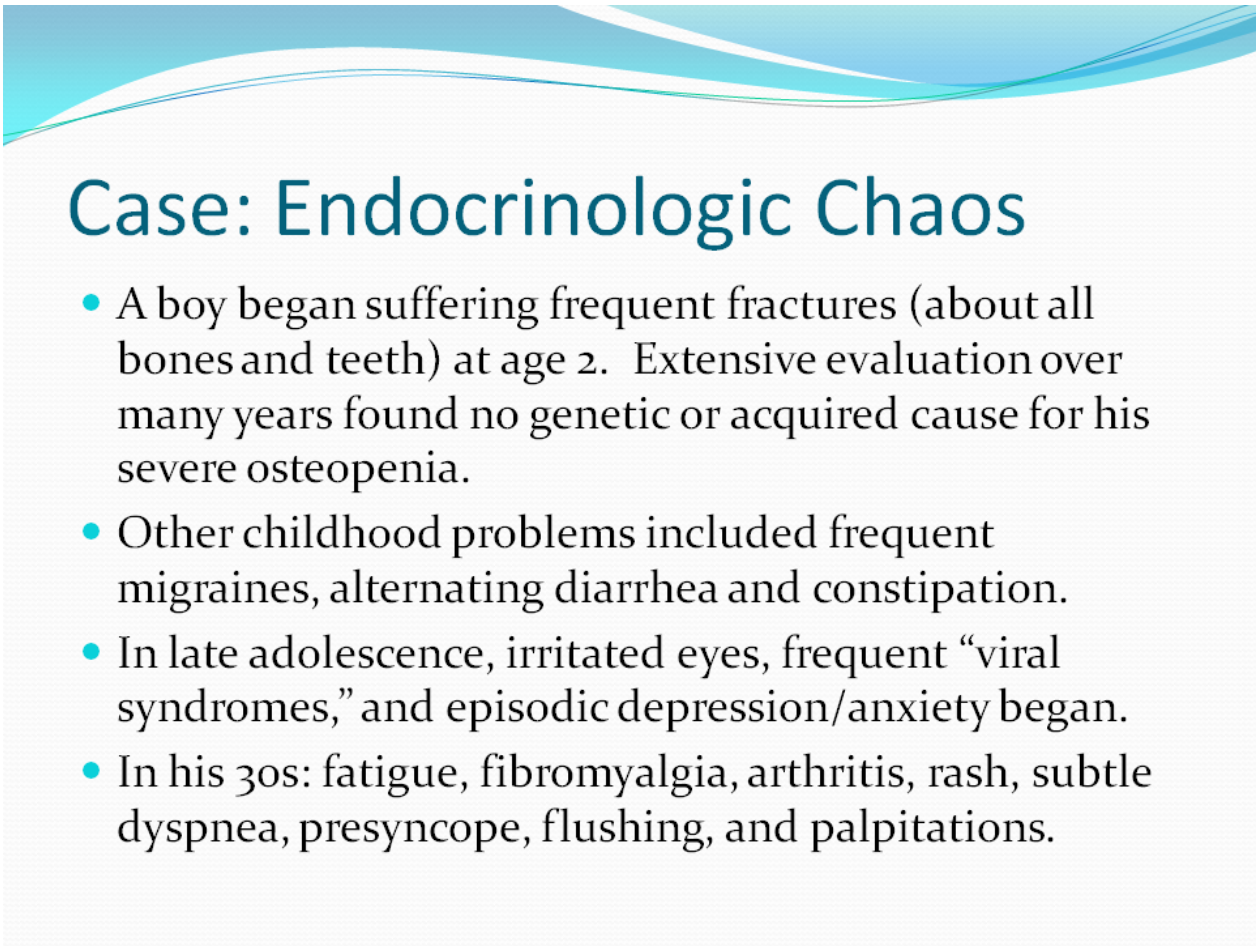
[Slide 96: MCAS: Presentation.]

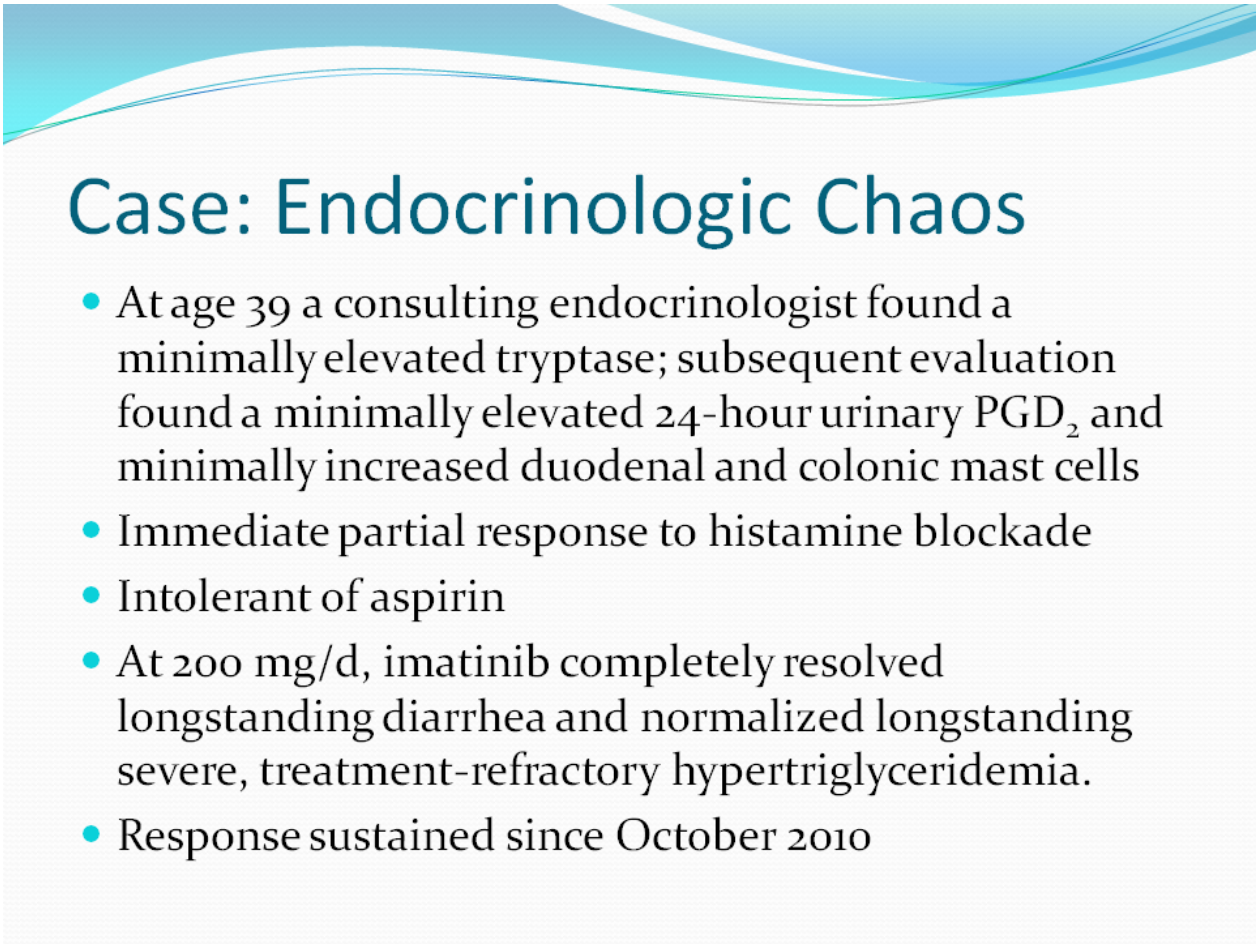


The endocrinologic issues are wide-ranging, too, and include delayed puberty, delayed menarche, endometriosis, irregular menses, bone problems (too much bone and/or too little bone), and too much or too little thyroid function. Hyperferritinemia can be present to an astounding degree, and it's likely inflammatory. (Ferritin itself is a known mast cell mediator product, too.) Electrolyte abnormalities and lipid abnormalities are often present, and sometimes pretty significant hypertriglyceridemia can be seen such as in this (next) patient.

Dr. Sibbald: Of the people here, are there any of these abnormalities that would clue you in to anything specifically? (All indicated No.)

[Slides 97-98: Case: Endocrinologic Chaos.]





Dr. Afrin: A boy began suffering frequent fractures at age two. No genetic or acquired cause could be found for the severe osteopenia. Multiple other problems occurred throughout childhood and just got worse and worse as the decades went on. Finally an endocrinologist checked a serum tryptase and found it to be minimally elevated. I then found a minimally elevated urinary PGD_2 and slightly increased GI tract mast cells. He had immediate partial response to histamine blockade. He was intolerant of aspirin. He went on to a trial of low-dose imatinib, which very interestingly not only completely resolved his longstanding diarrhea but also completely resolved his longstanding severe hypertriglyceridemia (about 1800 and utterly treatment refractory) virtually overnight.

David Girvin: Do you know what happened to his heparin? Did you measure the heparin after the treatment?

Dr. Afrin: I did not.

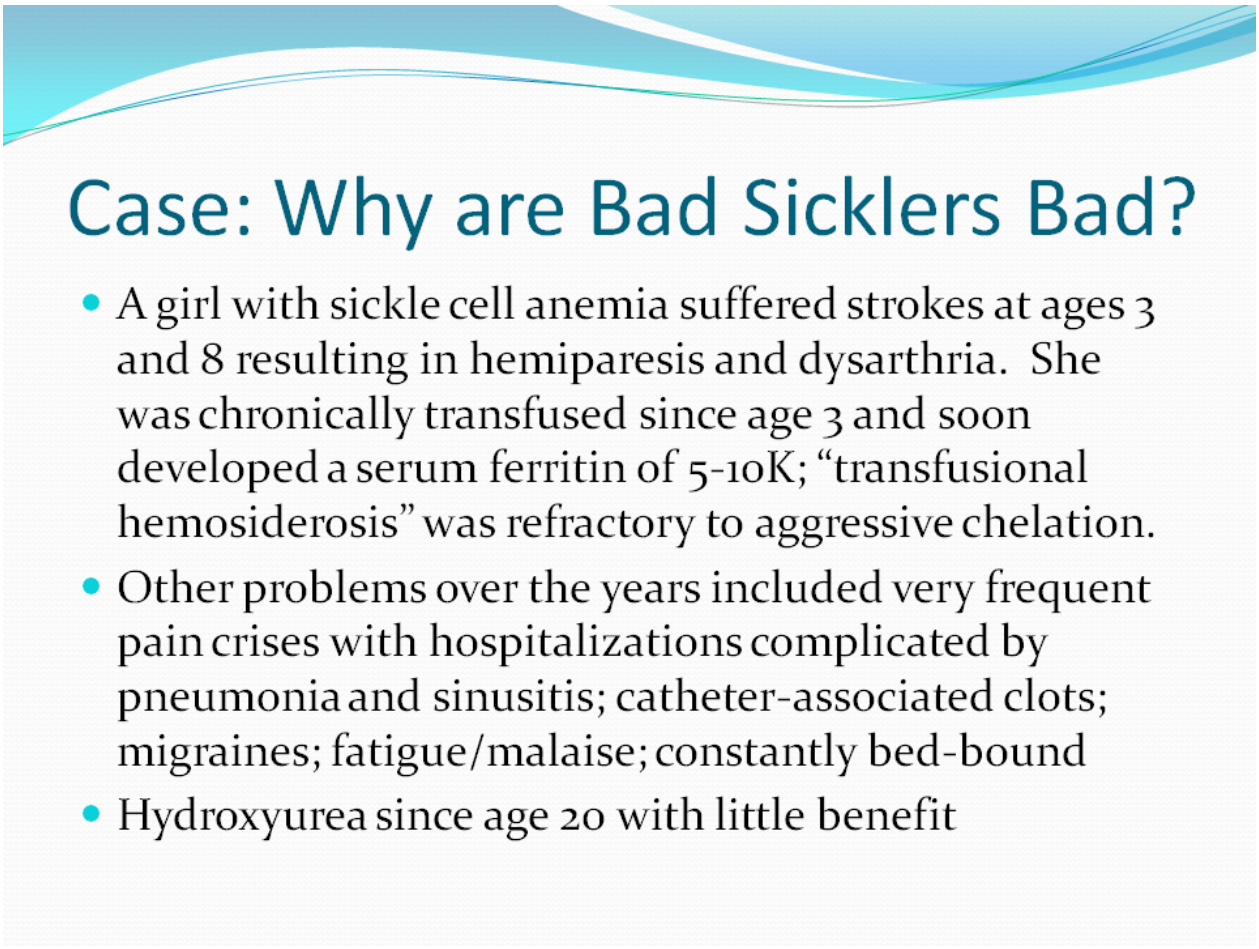
David Girvin: Have you had any (idea) exactly whether his heparin has gone down after treatment?

Dr. Afrin: No, and in fact in most of these patients I have not found utility in following the diagnostic marker levels.

David Girvin: I'm just curious whether there's a correlation between marker levels and symptoms or findings in other labs.

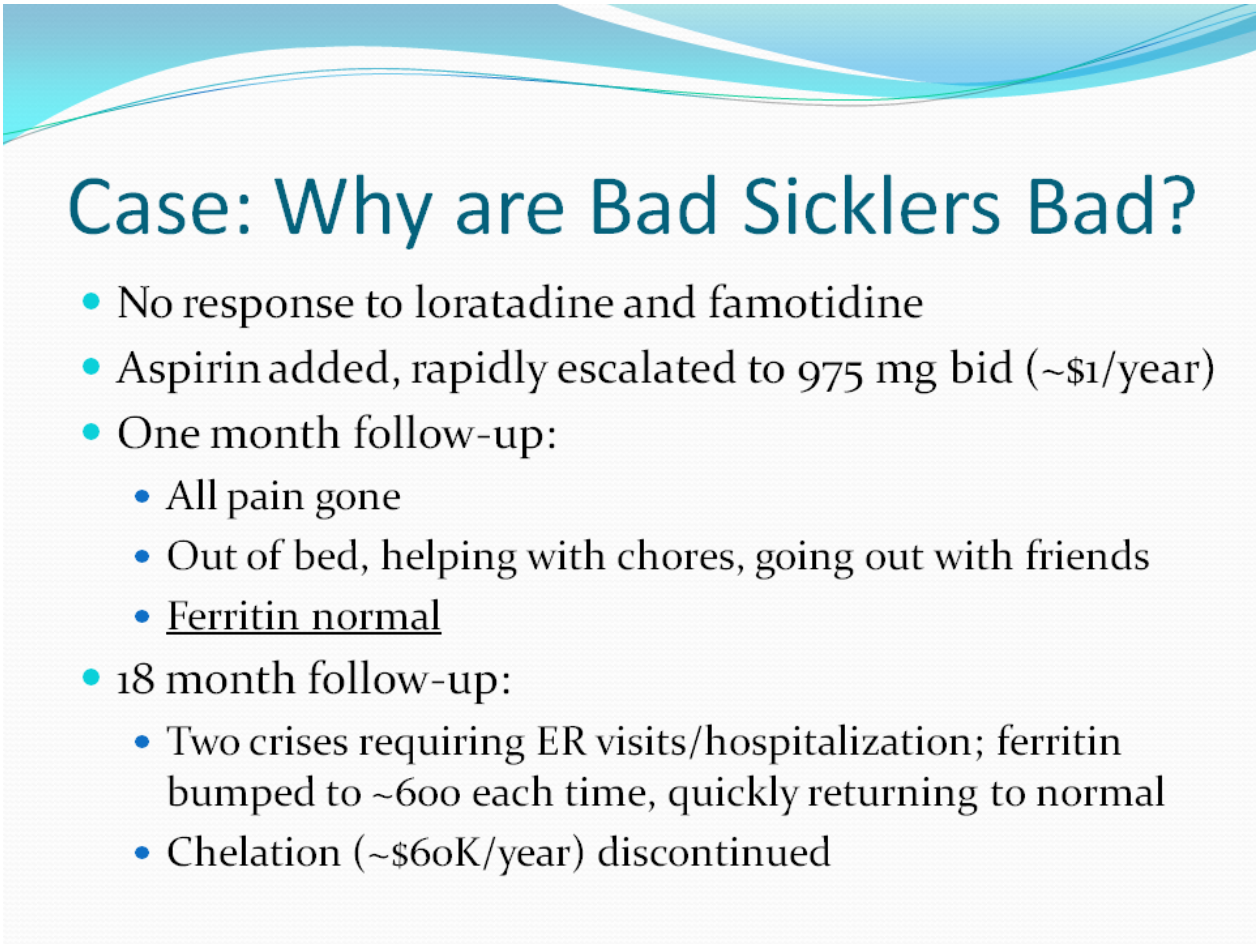
Dr. Afrin: Currently that doesn't appear to be the case.

[Slides 99-101: Case: Why Are Bad Sicklers Bad?]



Case: Why are Bad Sicklers Bad?

- Chronic lab abnormalities included modest thrombocytosis, monocytosis, eosinophilia, basophilia, elevated PT/PTT; periodic severe anemia; ANA 1:640
- Imaging showed chronic modest retrocrural adenopathy and a normal-sized spleen
- At age 32 she developed severe whole back pain refractory to multiple pain medications
- Serum CGA 89 ng/ml (normal 0-50), plasma tryptase, histamine and $uPGD_2$/NMH all top normal

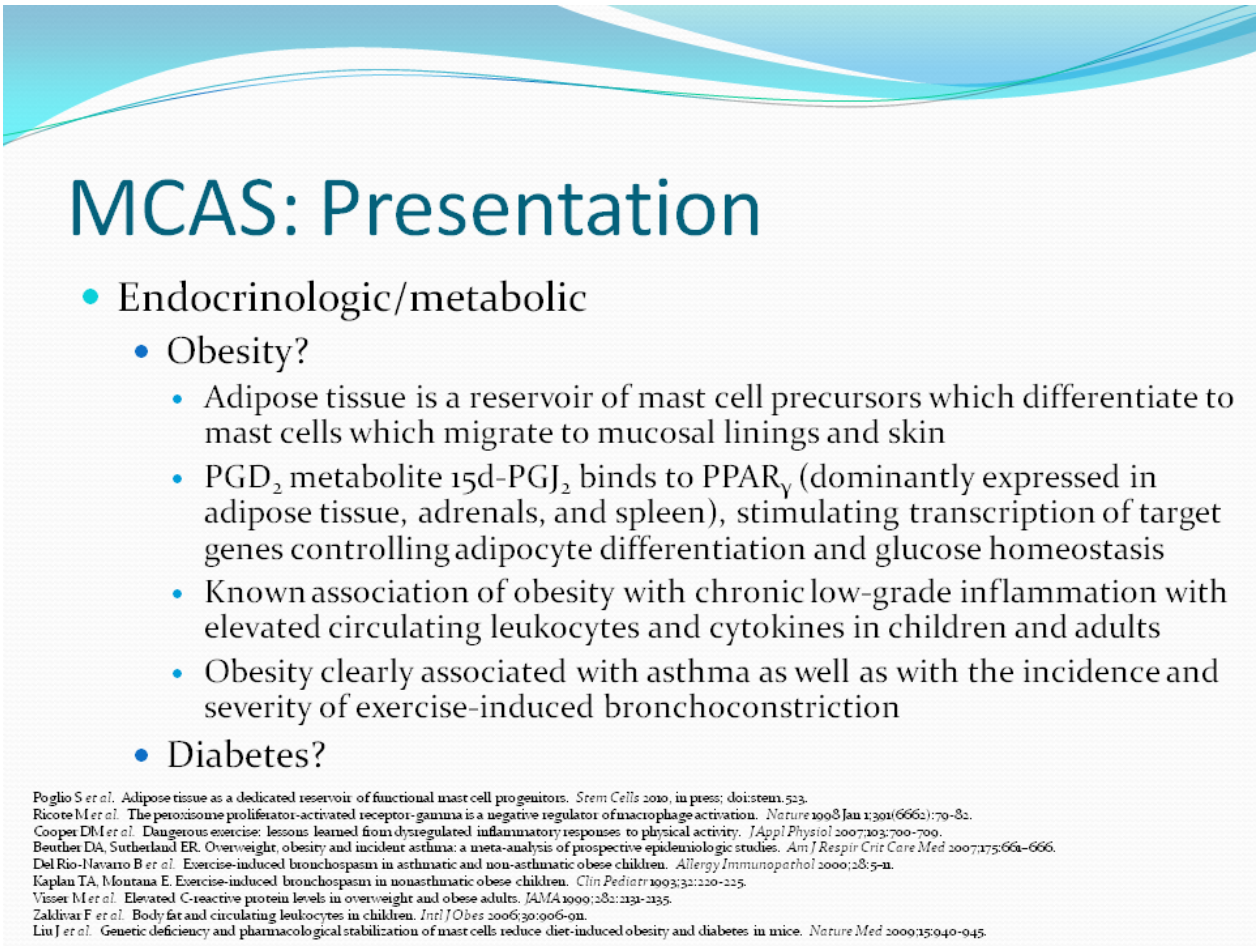


Dr. Afrin: The vast majority of sickle cell anemia patients are "good sicklers" with only an occasional sickle cell pain crisis; they rarely get hospitalized and are able to be productive members of society. The hematologist's bane, however, is the "bad sickler." Bad sicklers are the sickle cell anemia patients who seem to incur many of the known complications of sickle cell disease beyond just the painful vaso-occlusive crises. The question, though, is this: if all sickle cell anemia patients have exactly the same beta-globin mutation, then why do they segregate into good sicklers and bad sicklers? Logically, there must be something beyond the beta-globin mutation causing the bad sicklers to go bad.

A girl with sickle cell anemia suffered strokes at ages 3 and 8 –right away defining her as a bad sickler – resulting in chronic transfusion therapy since age 3 (which obviously did nothing to prevent the stroke at age 8) and soon developed a serum ferritin that was wildly varying between 5,000 ng/ml and 10,000 ng/ml from one determination to the next, with no correlation at all to her transfusion history. The hyperferritinemia, long attributed to her transfusion therapy, was utterly refractory to aggressive chelation with both Desferal and Exjade. Other problems, too, developed over the years, including pneumonias. Interestingly, her pneumonias were never really classic pneumonias. They

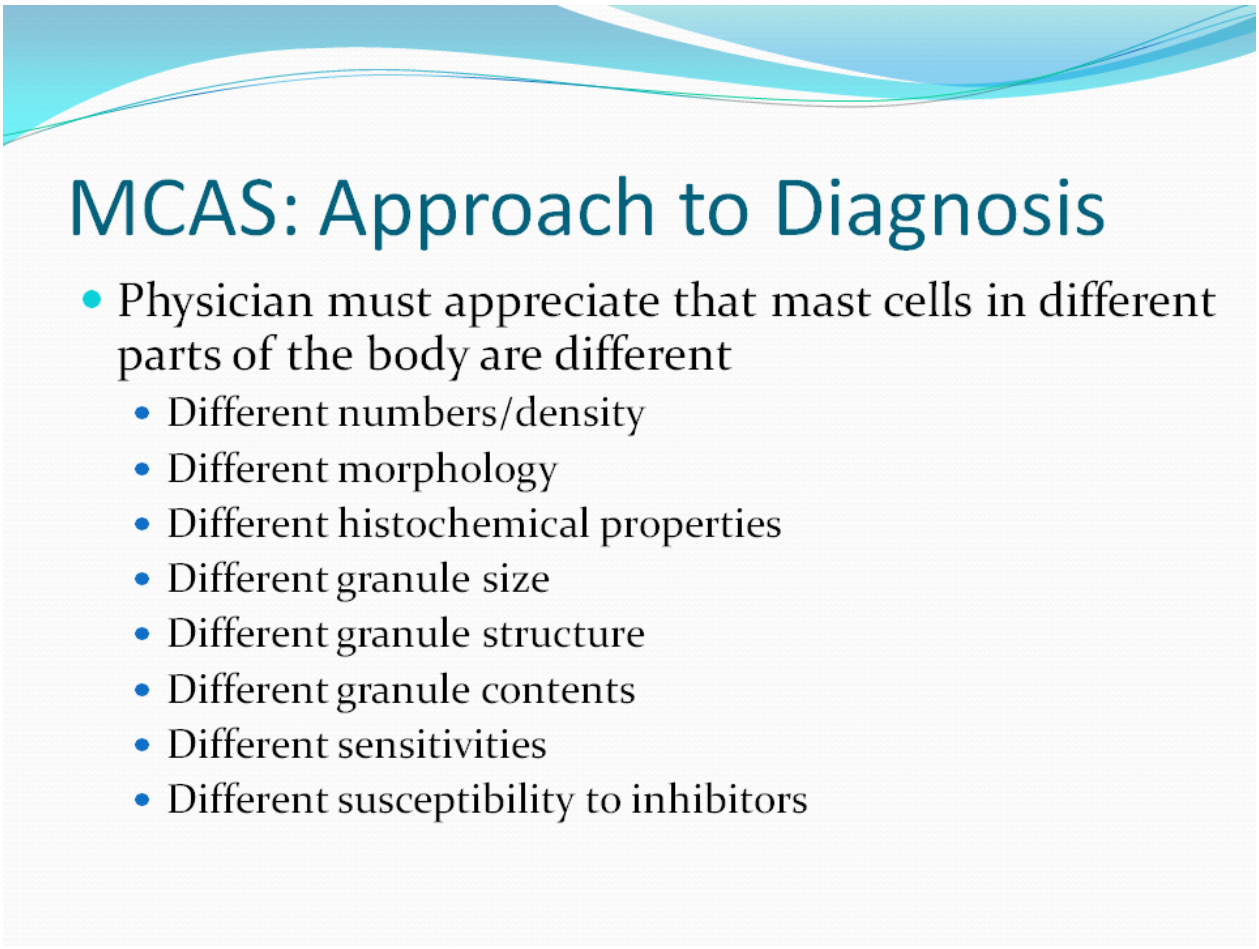
were always radiographically diagnosed as a patchy inflammation in one lobe or another, basically just inflammation in the lungs. It was clinically interpreted as pneumonia. She was constantly bed-bound and just couldn't do anything. She was severely malaised. Hydroxyurea didn't help. She had multiple chronic lab abnormalities not attributable to sickle cell disease. I started to get the gist that there was something else going on, because sickle cell anemia couldn't explain many of her problems. For example, how could a 32-year-old sickler have a normal sized spleen? In sickle cell anemia, the spleen has auto-infarcted and shriveled virtually to the vanishing point by the time you're a few years old. And yet multiple physicians, multiple radiologists, never picked up on how severely abnormal her normal-sized spleen was. So finally she got severe whole back pain, refractory to multiple pain medications, and she came to me. I thought the pattern here was such that it couldn't be sickle pain, i.e., there's no question you have sickle cell anemia, but sickle cell anemia doesn't behave like this, so you must have something else, and what might that be? I began looking for MCAS and quickly found multiple elevated mediators. She did not respond to antihistamines, but then I added aspirin. You start low because of the risks of NSAIDs triggering the disease to flare, but then quite often you're able to ramp the NSAID dose up pretty high. Dr. Jack Roberts at Vanderbilt, in some of his patients, goes as high as 1300 mg four times daily, targeting a plasma salicylate level of 20-30 mg/dl. I don't go that high. From what I've observed, if you're not getting better by around 1300 mg 2-3 times daily, then aspirin is not going to be of significant help. Regardless of the dose, aspirin is extremely cheap. She achieved excellent control and seemed to transform overnight from a "bad sickler" to a "good sickler," bounding out of bed, going on shopping and fishing trips, helping with family chores, basically just being a very happy person, and by the very next determination her ferritin of 5,000 ng/ml had fully normalized (under 300 ng/ml) and has remained normal ever since except for two pain crises (sickle cell? MCAS? both?) for which she was hospitalized. In each of these two crises the ferritin bumped up to around 600 and then as soon as the crisis settled down, the ferritin went back to normal. Her chelation treatment, which she had received for many years and which was costing $60,000 a year, was discontinued.

[Slide 102: MCAS: Presentation.]



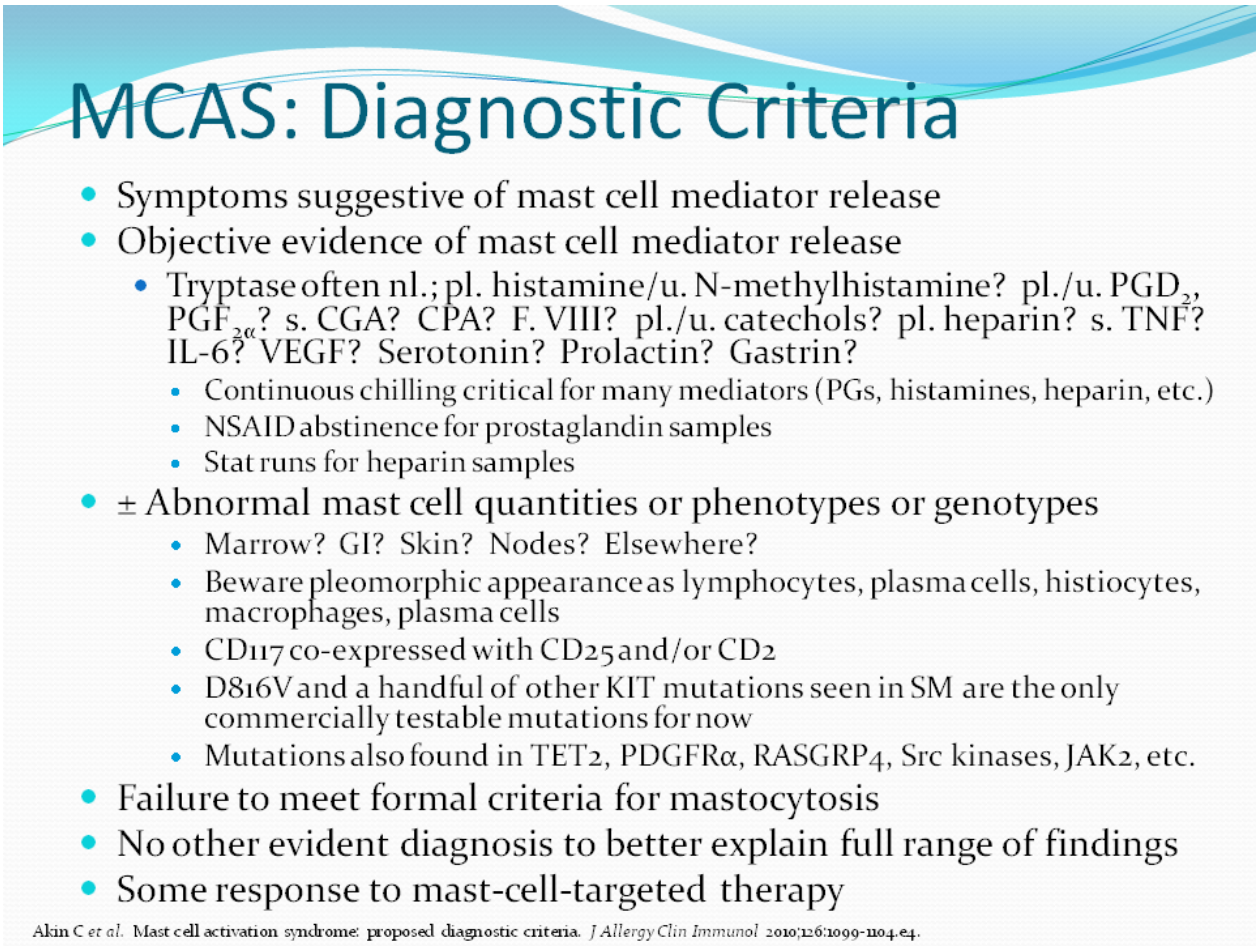
One has to wonder whether there is a connection between the epidemic of obesity and mast cell disease. I don't have nearly enough time to go into all of the biology here, but there are some very interesting potential links. Adipose tissue is a known reservoir of mast cell precursors. PGD_2 is intimately involved in at least two key lipid management pathways. There is a known association of obesity with low grade inflammation, though we don't yet know where the inflammation is coming from. There is now a mouse model in which a particular flavour of mast cell disease clearly leads to a classic type 2 diabetic phenotype. So there are potential links between MCAS and diabetes as well.

[Slide 103: MCAS: Approach to Diagnosis]



Physicians have to appreciate that mast cells in different parts of the body are different in numbers, density, morphology, granule size, granule content, sensitivities, and different susceptibility to different inhibitors, so to diagnose it…

[Slide 104: MCAS: Diagnostic Criteria.]



…you must have symptoms of mast cell mediator release and you have to find objective evidence of mast cell mediator release. There is no standard approach to doing this. I can't give you a literature-based recommendation on how to do this. I can tell you what my practice is, but it would take more time than we have available right now, so I'll save that for later offline if you're interested. I do check for some of these mediators in initial screens, and if it all comes back negative, then I have a few others I check. There are tricks to running these. Some are technically challenging and/or expensive to run. For PGD_2, histamine, and heparin, you have to have continuous chilling including, ideally, pre-chilling the specimen container, keeping the container chilled throughout collection, and transporting the specimen on ice to the lab. Some labs are not capable of running some tests and have to send the specimen out to another lab, so care in packing is required to ensure the specimen stays cold for the duration of the long trip.

Dr. Sibbald: That ain't gonna happen…

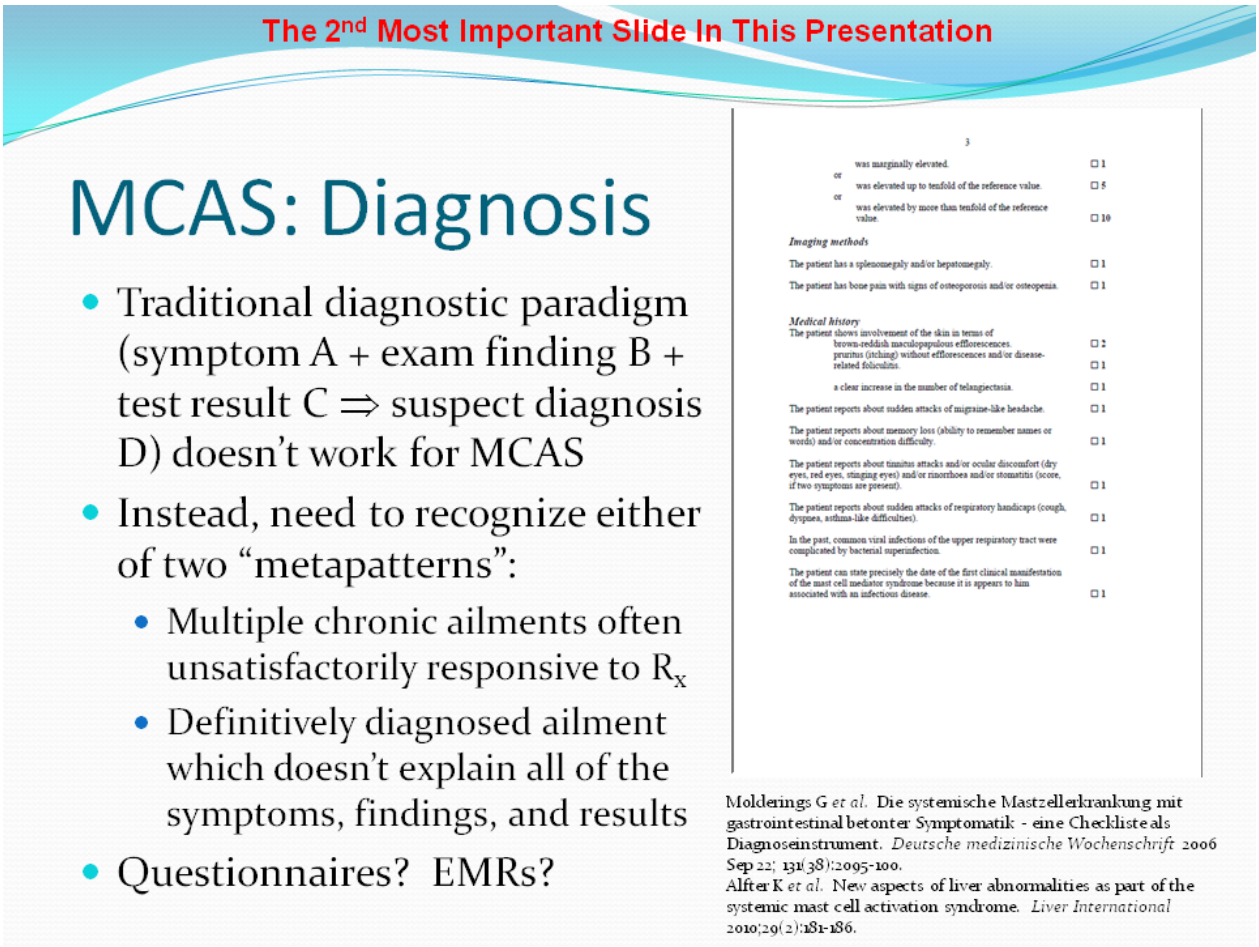
Dr. Afrin: But it can happen….

Dr. Sibbald: Yeah, but it isn't going to happen here.

Dr. Afrin: But it does happen if you take enough time… it's difficult…you have to avoid NSAIDs if you're going to go looking for prostaglandins, and if you're going to do heparin sampling, you must run it stat, so if the lab that's drawing the blood sample for the plasma heparin level can't run the level on-site, then it's not worth drawing the sample, let alone still trying to run the test at a remote reference lab. This need for stat processing ties into why many of these patients have a normal PTT despite an abnormal heparin level.

You can, too, if you want, go hunting for the abnormal cells themselves. I do this if either the patient himself has doubts about the diagnosis or more commonly when both the patient and I know that he's going to run into trouble with other physicians not believing he has a diagnosis based solely on symptoms and mediator levels because many physicians are not trained to understand what an abnormal urinary PGD_2 means, but if you show a physician a pathology report that shows abnormal mast cells, then he may believe it. There has to be failure to meet full criteria for mastocytosis, there has to be no other evident diagnosis that better explains the full range of findings and there has to be some response to mast cell targeted therapy. So, on to the second most important slide in this presentation….

[Slide 105: MCAS: Diagnosis.]



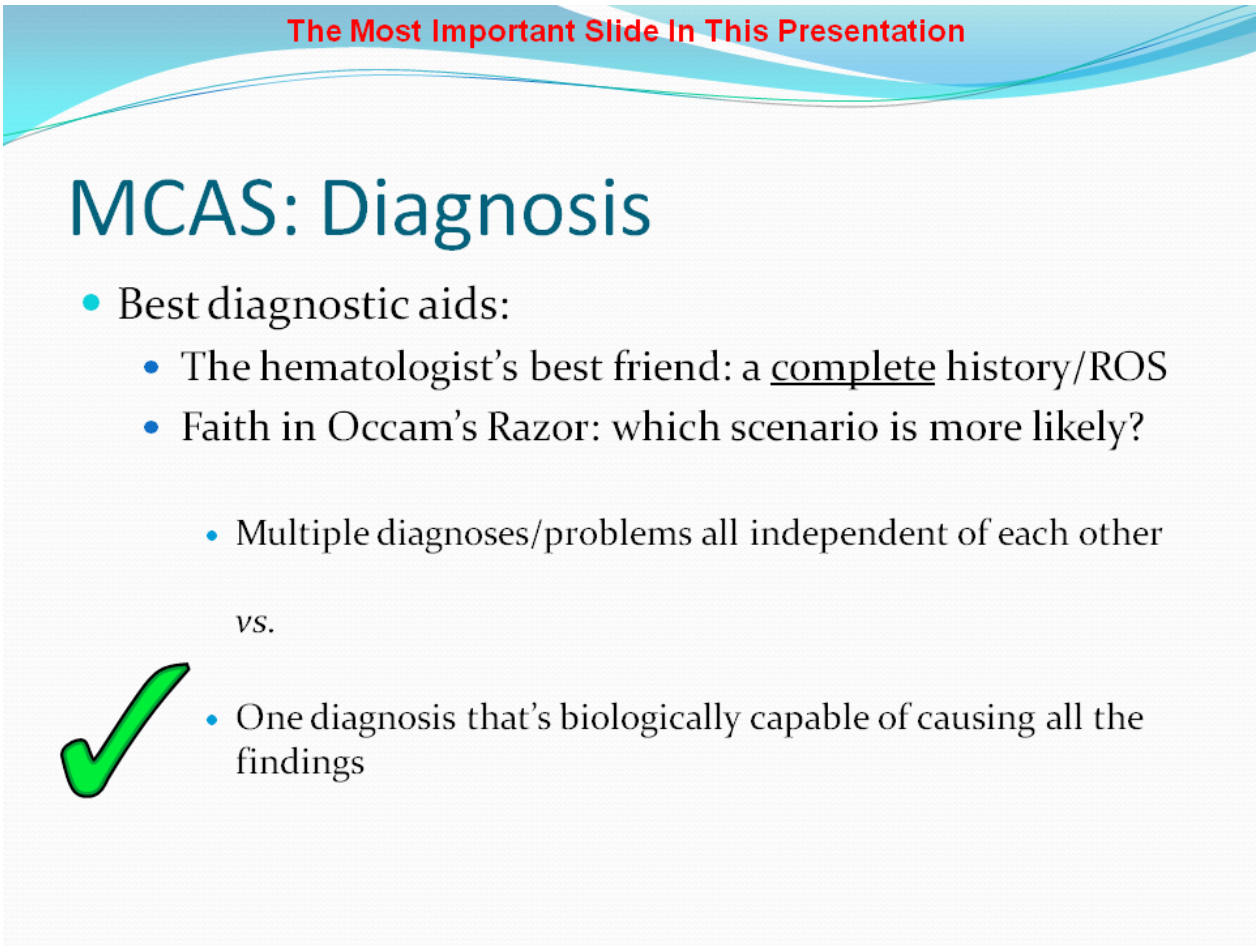
What we learned in medical school about how to diagnose, that symptom A plus physical exam finding B plus test result C should lead you to suspect diagnosis D, utterly fails here because of the extreme heterogeneity of the presentations. Instead, what I have found most useful is to look at the big picture. In diagnosing MCAS I'm looking for either of two of what I'm calling metapatterns – either a situation of multiple chronic ailments often unsatisfactorily responsive to treatment, or a situation of a definitively diagnosed major illness, say a lymphoma, but that diagnosis is insufficient to explain a number of the patient's other symptoms (for example, a lymphoma patient who is routinely having syncope). I don't know if there's a best way to help the medical profession get better at recognizing these metapatterns. Possibilities include questionnaires for patients, and actually Dr. Molderings in Bonn has developed and validated a questionnaire. However, his group focused mainly on patients with predominantly GI symptoms, so I don't know if his questionnaire is going to be valid for the full spectrum of mast cell activation syndrome patients. Alternatively, we might be able to program our electronic medical record systems to watch for these subtle

multisystem patterns that could then alert the physician to the possible presence of MCAS, but that's likely many years off.

David Girvin: You ask about how you enhance the medical community's understanding about this disease. It's been my experience that the emergency doctors, after you explain it as an informed citizen, they'll go to Wikipedia and Google, if those two points were the first edited points that grab attention – the number of physicians that come to me afterwards and said you were right x hours later and I know they looked it up. But it's the WHO that irritates it. And it doesn't make any sense relative to that clause….I'm just saying that your community looks…Googles…and it's an opportunity for something that might be worthwhile as opposed to being the bane of all physicians.

Dr. Afrin: That's a decent suggestion. We're getting close to the end here.

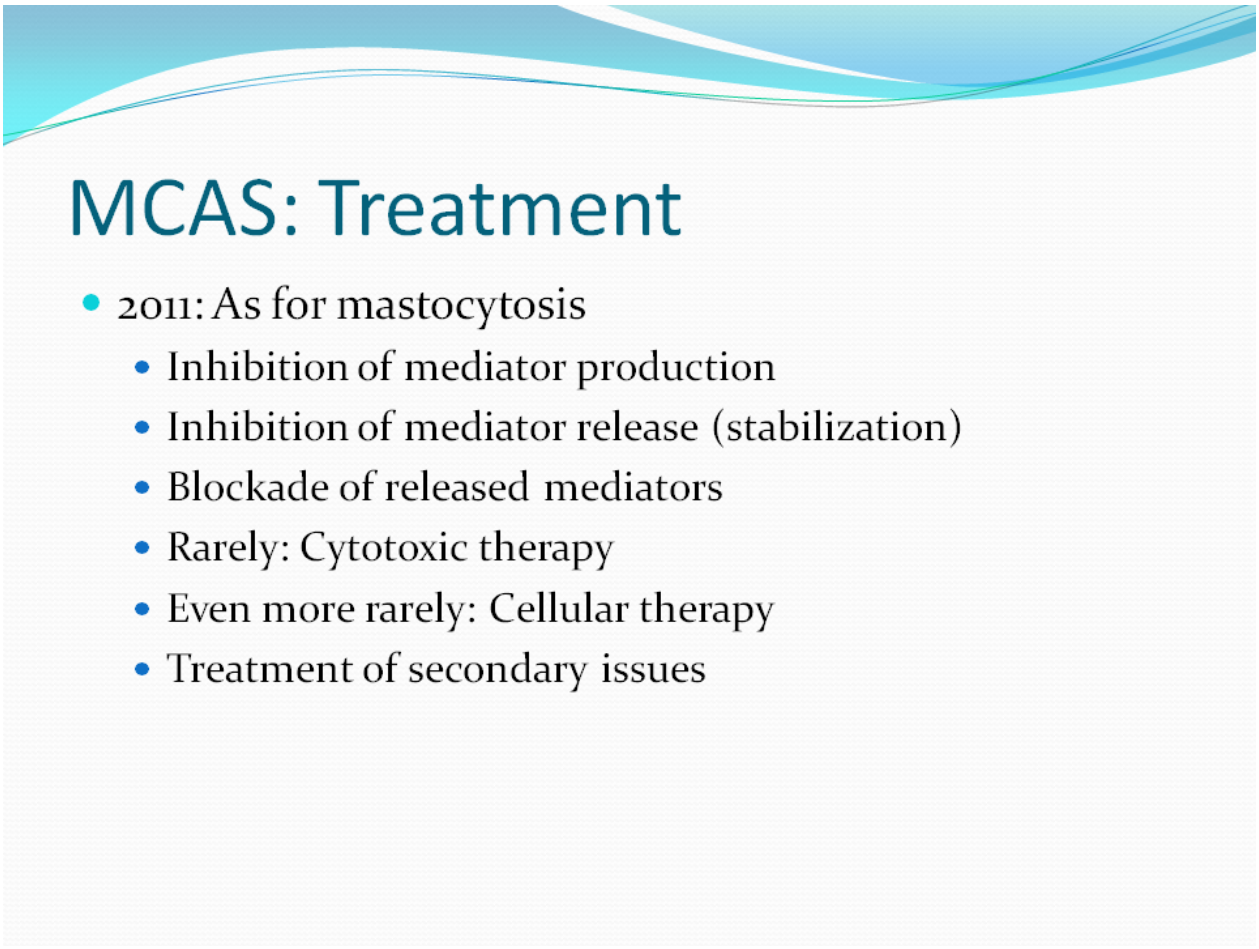
[Slide 106: MCAS: Diagnosis.]



The hematologist's best friend – actually, any doctor's best friend – is the best way to diagnose this, namely, a complete history and review of systems. And instead of just giving lip service to Occam's Razor, we need to restore our faith in Occam's Razor, because what is more likely: does the patient have multiple diseases all independent of one another, or does the patient have one "root" disease that is biologically capable of causing all of the observed problems? There are exceptions to Occam, of course. For example, people with inborn genetic diseases such as sickle cell anemia, Ehlers-Danlos, or Charcot-Marie Tooth certainly have those diseases, but such unlucky draws in the genetic lottery of life certainly don't make such patients immune to any other disease, and if MCAS truly is a prevalent disease, then it is much more likely than not that one would be able to relatively easily find such congenitally afflicted patients whose full spectrum of illness includes not only the consequences of their inborn problem but also the consequences of MCAS. Similarly, there are people who acquire acute and chronic infectious illnesses due in no way to an MCAS-induced immune deficiency but instead just classic infectivity (for example, a bite from a malarial mosquito). Again, if MCAS truly is a prevalent disease, then it is much more likely than not that one would be able

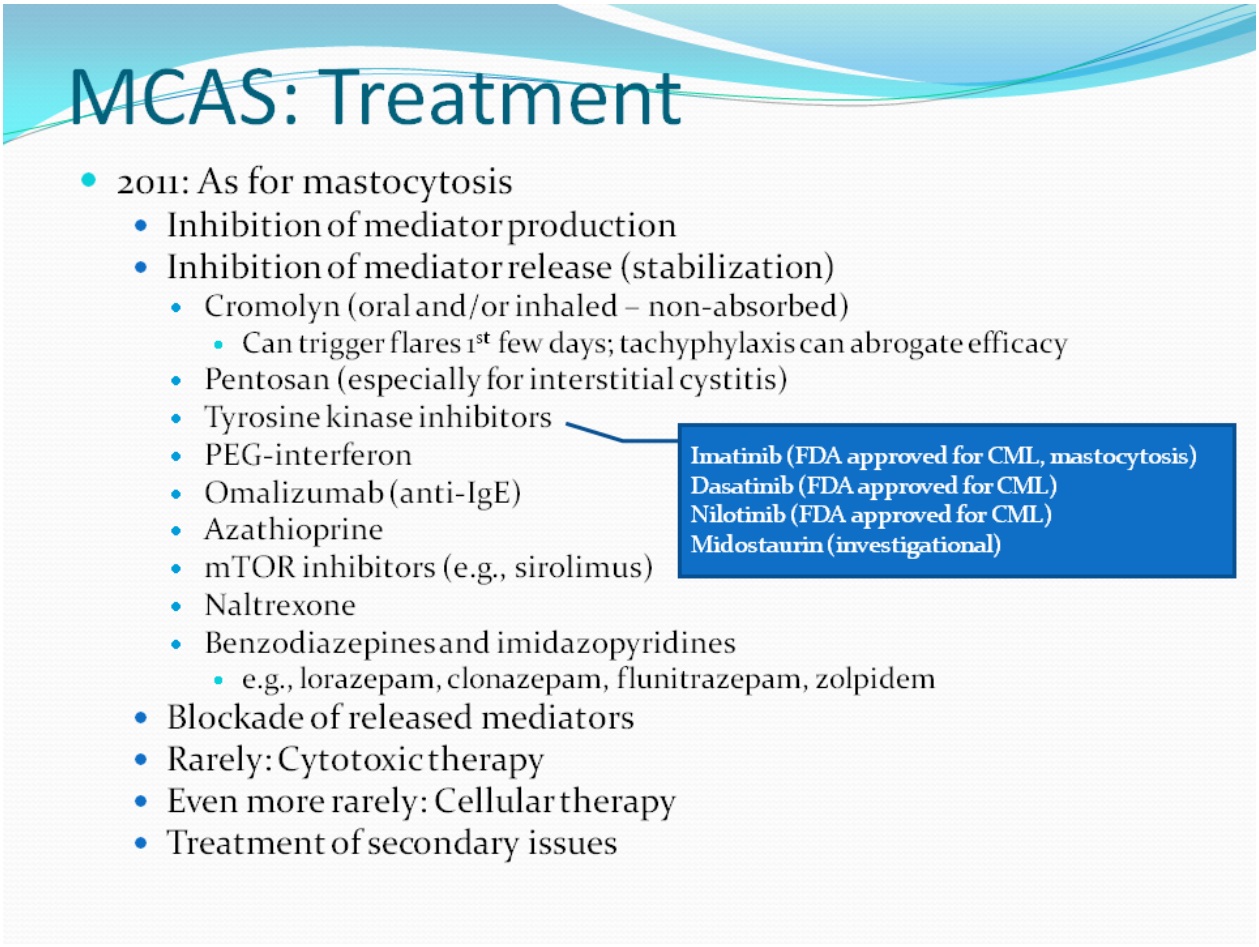
to relatively easily find such infectiously afflicted patients whose full spectrum of illness includes not only the consequences of their infection but also the consequences of MCAS (which may be intensified by the infection). My point is that although the clinical heterogeneity of MCAS makes it tempting to ascribe – and even Occam favors ascribing – every symptom and finding in an MCAS patient to MCAS, clinicians who deal with MCAS must always remain alert to the prior presence, or development, of other, true non-MCAS illnesses (whether contracted due to MCAS-induced proclivities or not).

[Slides 107-114: MCAS: Treatment.]



MCAS: Treatment

- 2011: As for mastocytosis
  - Inhibition of mediator production
    - Steroids, NSAIDs
    - Possibly also IMIDs
  - Inhibition of mediator release (stabilization)
  - Blockade of released mediators
  - Rarely: Cytotoxic therapy
  - Even more rarely: Cellular therapy
  - Treatment of secondary issues


MCAS: Treatment
2011: As for mastocytosis
Inhibition of mediator production
Inhibition of mediator release (stabilization)
Cromolyn (oral and/or inhaled – non-absorbed)
Can trigger flares 1st few days; tachyphylaxis can abrogate efficacy
Pentosan (especially for interstitial cystitis)
Tyrosine kinase inhibitors
PEG-interferon
Omalizumab (anti-IgE)
Azathioprine
mTOR inhibitors (e.g., sirolimus)
Naltrexone
Benzodiazepines and imidazopyridines
e.g., lorazepam, clonazepam, flunitrazepam, zolpidem
Blockade of released mediators
Rarely: Cytotoxic therapy
Even more rarely: Cellular therapy
Treatment of secondary issues
Imatinib (FDA approved for CML, mastocytosis)
Dasatinib (FDA approved for CML)
Nilotinib (FDA approved for CML)
Midostaurin (investigational)

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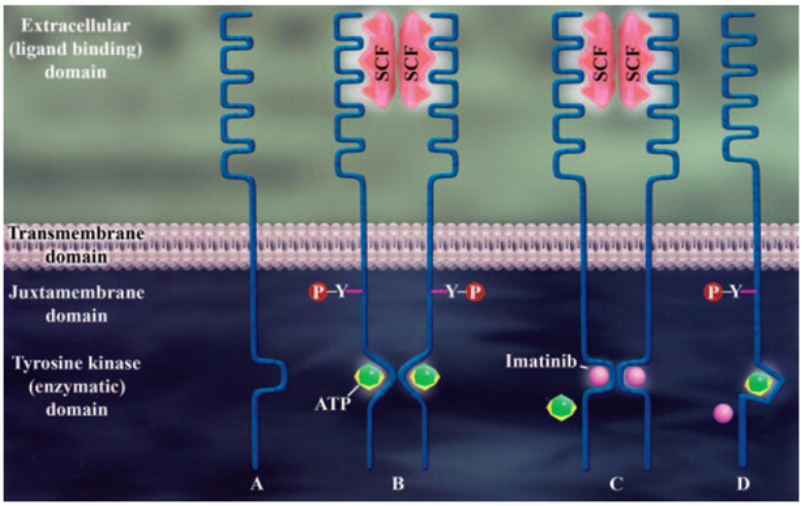


FIG 1. Kit monomer exists in an inactive conformation when unbound to its ligand *(A)*. Cross-linking of Kit by SCF induces a conformational change in the kinase domain, which allows binding of adenosine triphosphate and phosphorylation of tyrosine residues *(B)*. Imatinib binds to the inactive conformation of Kit and inhibits binding of adenosine triphosphate *(C)*. Mutations in enzymatic site or tyrosine kinase domain of the molecule render resistance to imatinib by interfering with its binding to Kit *(D)*.

MCAS: Treatment

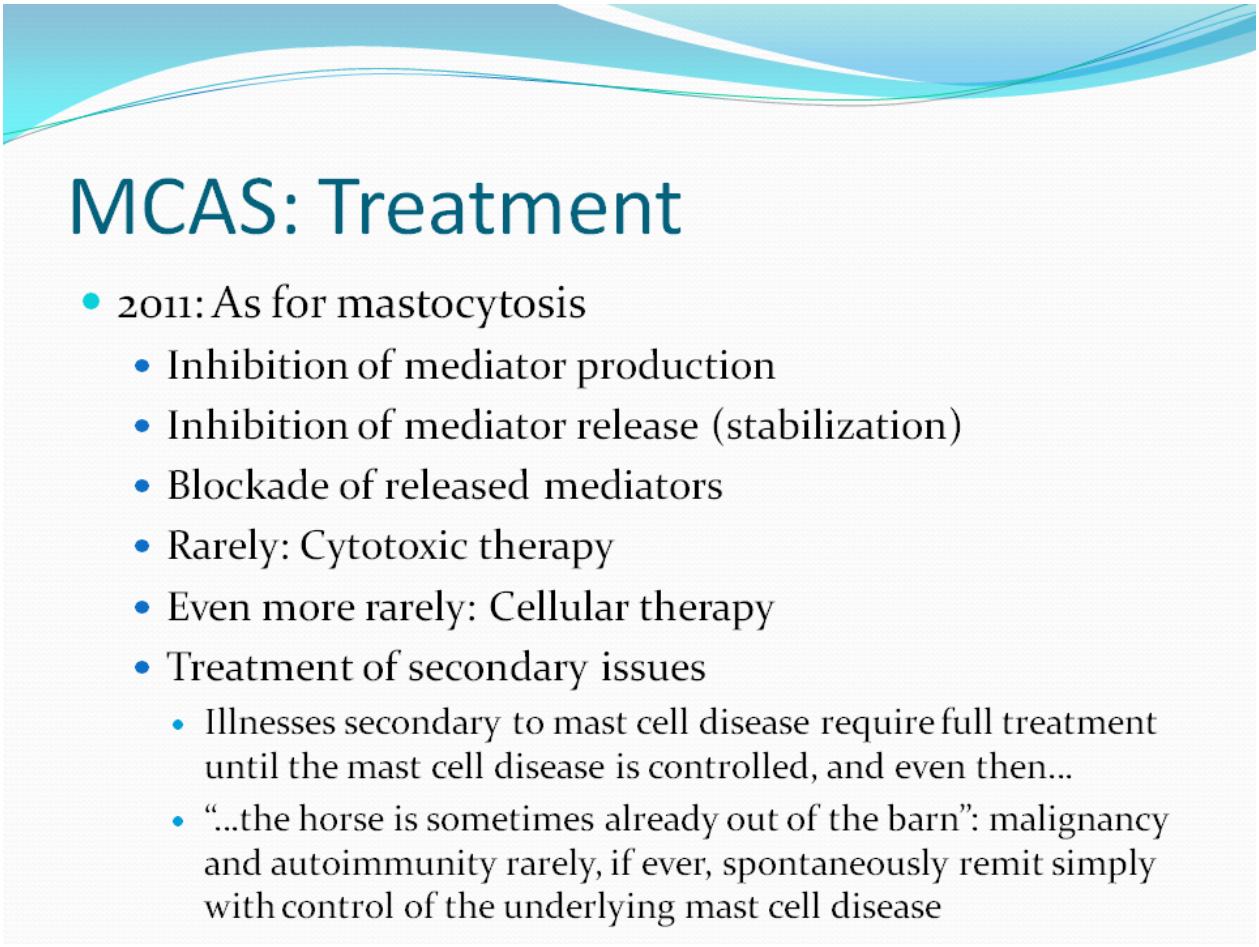
- 2011: As for mastocytosis
  - Inhibition of mediator production
  - Inhibition of mediator release (stabilization)
  - Blockade of released mediators
    - Antihistamines
      - Often impressive benefits even absent rhinosinusitis and dyspepsia
      - Can also stabilize mast cells via their autoexcitatory H_1/H_2 receptors
    - Leukotriene antagonists
    - Bisphosphonates, Ca++/vit. D, denosumab for osteoporosis/osteopenia
    - TNF antagonists (etanercept, adalimumab, infliximab)?
    - IL-1 antagonists (e.g., anakinra), IL-1β antagonists (e.g., canakinumab)?
    - No tryptase inhibitors have made it to phase 2 trials yet
  - Rarely: Cytotoxic therapy
  - Even more rarely: Cellular therapy
  - Treatment of secondary issues

MCAS: Treatment

- 2011: As for mastocytosis
  - Inhibition of mediator production
  - Inhibition of mediator release (stabilization)
  - Blockade of released mediators
  - Rarely: Cytotoxic therapy
    - Hydroxyurea, alkylators, taxanes, etc.
    - Fludarabine, cladribine, cytarabine, etc.
    - Alemtuzumab, daclizumab
  - Even more rarely: Cellular therapy
  - Treatment of secondary issues

MCAS: Treatment

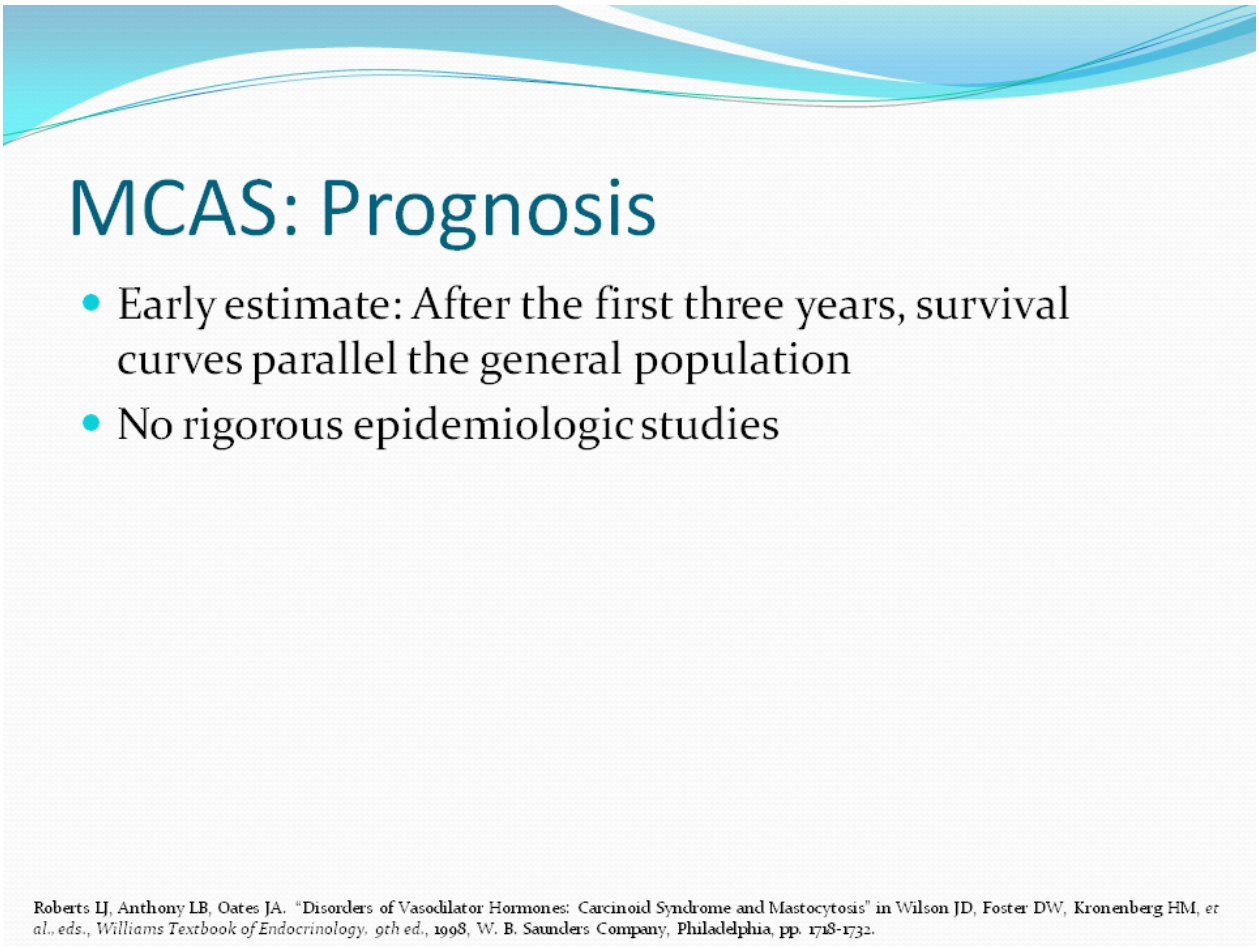
- 2011: As for mastocytosis
  - Inhibition of mediator production
  - Inhibition of mediator release (stabilization)
  - Blockade of released mediators
  - Rarely: Cytotoxic therapy
  - Even more rarely: Cellular therapy
    - Allogeneic stem cell transplantation
      - Rarely efficacious
  - Treatment of secondary issues



We don't have time for details, but shown on these slides are the general strategies for treatment of MCAS. You can inhibit mediator production, and there are various approaches to doing that. You can inhibit mediator release or stabilize the mast cell, and there are a variety of treatments for doing that. You can block the mediators after they've already been released (for example, with antihistamines). (By the way, there are both H_1 and H_2 receptors on the mast cell surface. There also are H_3 and H_4 receptors, but there seem to be far fewer of those receptors than of H_1 and H_2, and besides, we don't have any commercially available medications for blocking H_3 and H_4 receptors.) In any event, my point is that mast cells are autostimulatory.) You can undertake a usually futile effort to try to kill these cells, and you might get some brief improvement with medications like chemotherapy drugs, but by and large you can't kill these cells. And we don't seem to be able to kill them with cellular therapy, so where stem cell transplantation comes into play here is in patients who have gotten a bad leukemia because of this disease, making themcandidates for transplant, but the mast cell disease seems to essentially always persist post-transplant. I don't know of a single case where transplant has truly eradicated mast cell disease. And, finally, you can't forget that some of the secondary problems that arise with this disease, like autoimmunity or malignancy, are pertinent issues once they arise and can have serious

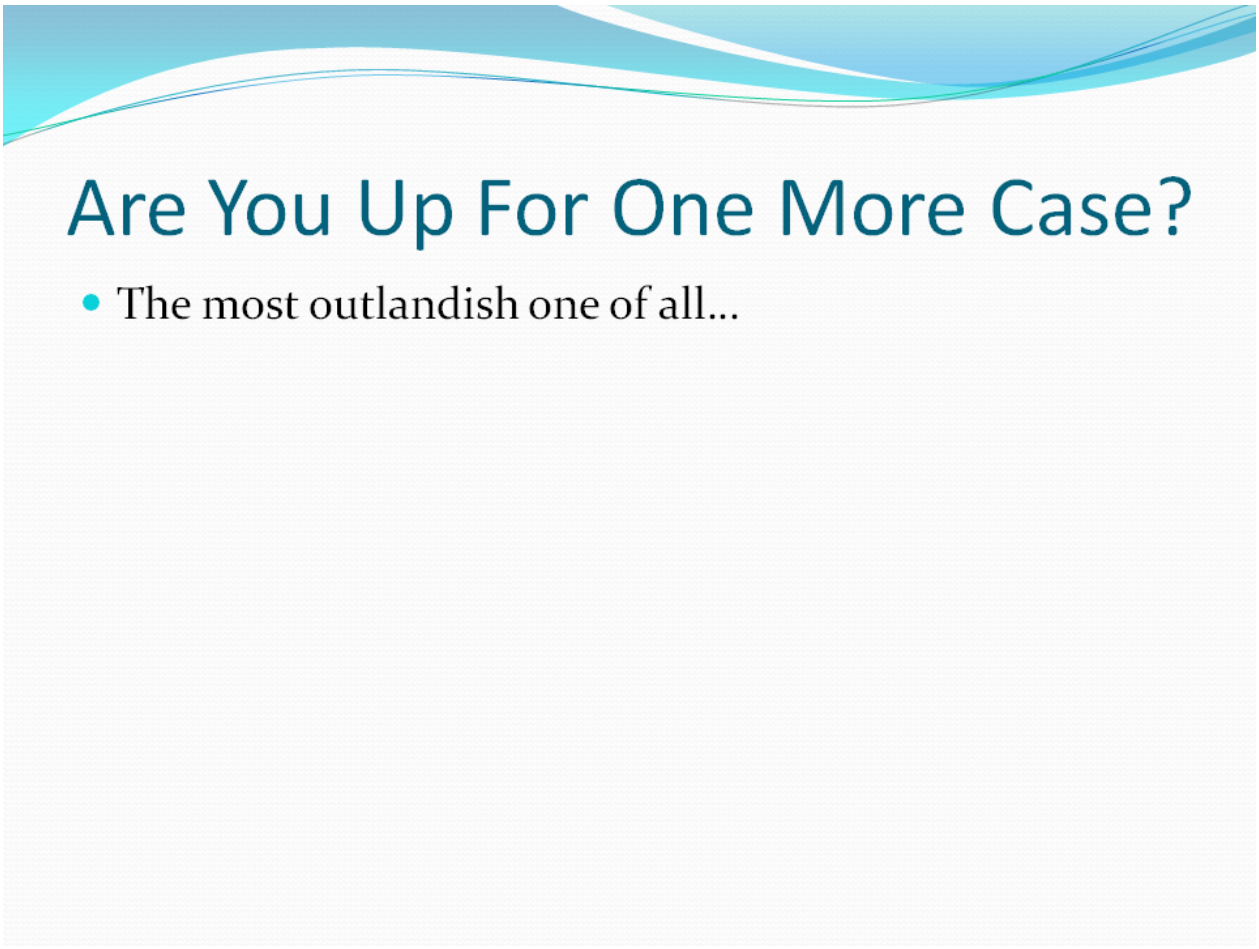
morbidities and must be treated for all intents and purposes as if they are independent problems. Even if you get the underlying mast cell disease under control, still the horse is already out of the barn, as they say, and you have to deal with that cancer.

[Slide 115: MCAS: Prognosis.]



We have essentially no credible data regarding prognosis in MCAS. There was one estimate by Dr. Jack Roberts of Vanderbilt back in 1998 that if you survive the first three years from diagnosis, it appears that your survival is going to be equivalent to the general population, but it's going to be a life of chronic misery until the disease gets properly diagnosed and treated. You can imagine the difficulty of trying to do rigorous epidemiological studies in a disease that is capable of presenting like anything.

[Slides 116-120: Case: Smoking is bad for you.]

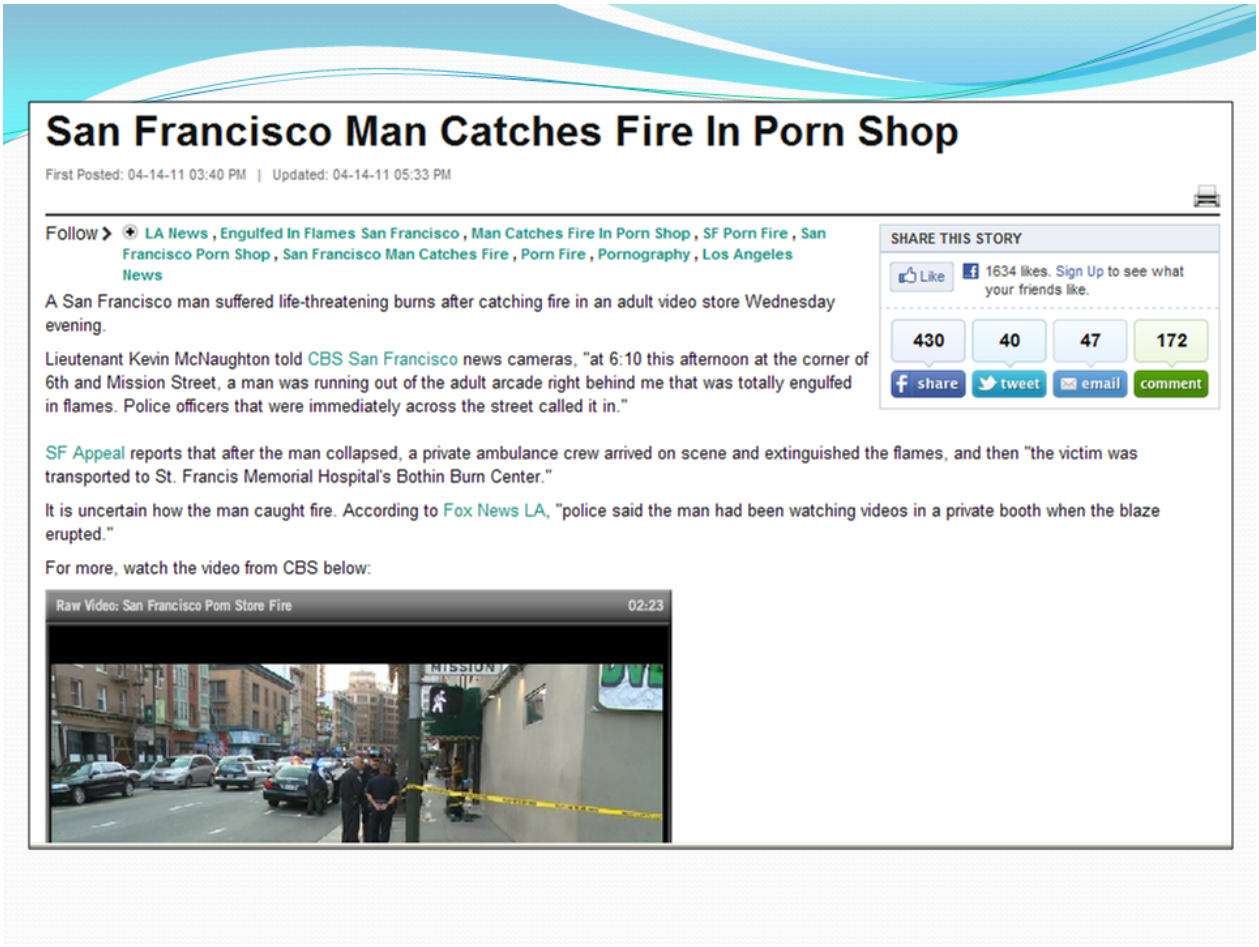


Case: Smoking Is Bad For You

- Soon after relocating from California to Louisiana in 1999, a 35 year old previously very fit man began suffering frequent idiopathic syncope, migraines, fevers, chills, pruritus, sweats, eye irritation, chest pain, GERD, nausea, diarrhea, abdominal pain, rashes, edema, neuropathy, cognitive dysfunction, odd medication reactions (e.g., Benadryl-induced pruritus).
- Relocated to South Carolina in 2001
- Multiple MIs and TIAs/CVAs over the next decade

Case: Smoking Is Bad For You

- Compound heterozygous MTHFR mutation and lupus anticoagulant found
- Referred in 2011 for further evaluation and management of hypercoagulability
- Additional history: new episodes since 2010 of spontaneous bruise-like welts (wife suspected of spousal abuse) and spontaneous emanation of smoke from all about his body
- Urinary PGD_2 500 ng/l (normal 100-280)
- Duodenal biopsy: increased mast cells (30/hpf)



San Francisco Man Catches Fire In Porn Shop

First Posted: 04-14-11 03:40 PM | Updated: 04-14-11 05:33 PM

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A San Francisco man suffered life-threatening burns after catching fire in an adult video store Wednesday evening.

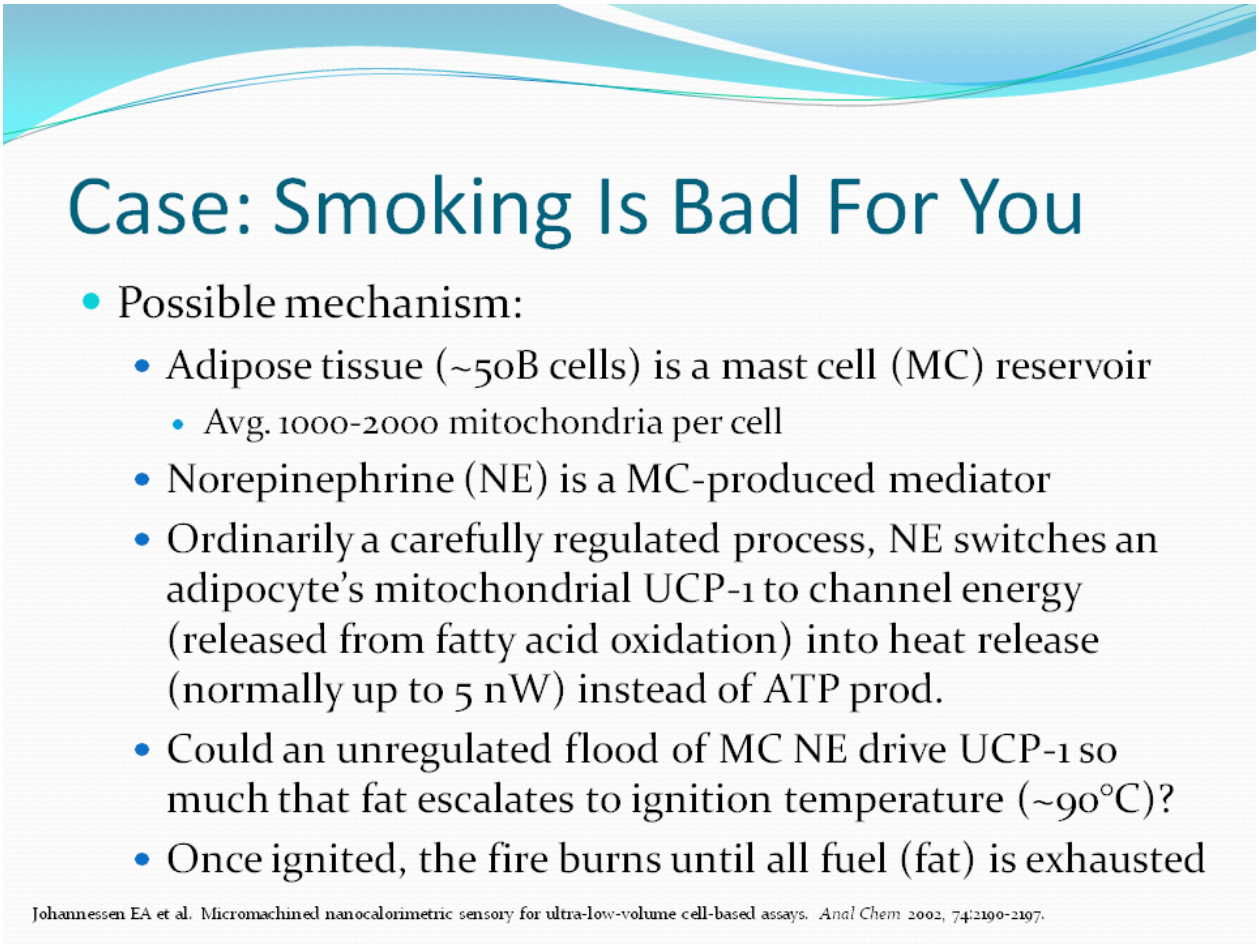
Lieutenant Kevin McNaughton told CBS San Francisco news cameras, "at 6:10 this afternoon at the corner of 6th and Mission Street, a man was running out of the adult arcade right behind me that was totally engulfed in flames. Police officers that were immediately across the street called it in."

SF Appeal reports that after the man collapsed, a private ambulance crew arrived on scene and extinguished the flames, and then "the victim was transported to St. Francis Memorial Hospital's Bothin Burn Center."

It is uncertain how the man caught fire. According to Fox News LA, "police said the man had been watching videos in a private booth when the blaze erupted."

For more, watch the video from CBS below:

Raw Video: San Francisco Porn Store Fire 02:23



OK, last case. This is really going to stretch the bounds of the range of illnesses that might be caused by MCAS. It certainly stretched my thinking about MCAS.

Soon after relocating from California to Louisiana in 1999, a 35 year old, previously very fit man began suffering frequent idiopathic syncope, migraines, fevers, chills, buritis, sweats, eye irritation, chest pain, GERD, nausea, diarrhea, rashes, abdominal pain, edema, neuropathy, cognitive dysfunction, and very odd medication reactions. He relocated to my state (South Carolina) a couple of years later and had multiple myocardial infarctions and strokes over the next decade, although none of them ever left any apparent residual damage. He was found on investigation for hypercoagulability to have an inborn mutation which can't really cause all of the heart attack and stroke problems he had had. Another potential source of hypercoagulability, a type of antibody known as lupus anticoagulant, was also found, but it's a bit odd for that disease to primarily manifest with heart attacks and strokes.

So he was referred to me earlier this year for further evaluation of his hypercoagulability. After I got all his history from him, and he saw that for the first time in many years there was a doctor who was taking the time to listen to his full history, he said, "I've got a

couple other things to tell you." These were not things that were in my review of systems at the time, but they are now. He said, "If I tell you this, you have to promise me first that you will not commit me to a psychiatric hospitalization." He was dead serious. He said that multiple other physicians had threatened him with psychiatric hospitalization after he revealed what he was about to tell me. So I of course promised him I wouldn't commit him, and he then told me he had begun having, earlier in the year – 2010 – episodes of spontaneous bruise-like welts erupting all over his body. In one of his visits to the ER for this, he was separated from his wife and he was quizzed about whether his wife was beating him.

And then he had a couple of episodes where he just started feeling very, very hot. Both of these times were when he was undertaking some physical activity. One time was a basketball game, and he had to sit down. He was a little foggy in the head, and a large crowd of people around him all asserted that smoke was emanating from all about his body. This wasn't vapour, this wasn't mist; it was smoke, as if from true combustion. In both episodes, the crowd around him took measures to cool him down. One time they put him in a pool, and another time they surrounded him with fans. They got him cooled down after about 30-60 minutes. He cooled down, stopped smoking, and the cognitive dysfunction abated.

Even without the episodes of spontaneous welts at some times and smoking at other times, just from his other symptoms, there was enough to suspect mast cell disease. I did the workup. His PGD_2 urinary was very high and a duodenal biopsy showed increased mast cells, so now the question becomes how one root process can explain everything. We can explain the welts and "bruises," as that could be due to heparin release into local tissues. He could be having flares of disease with localized eruptions of heparin. But what about the "smoking"?

It turns out there is a phenomenon called spontaneous human combustion. There have been approximately 100 cases reported over the last century. You will not find this in the medical literature because, I'm guessing, physicians simply can't believe this can happen, thus inclining medical journal editors to reject case reports of such incidents, but it's certainly in the forensic literature. There are about 100 cases very clearly documented over the last century or so. No cause has ever been found. It was not friction. If you read these cases, there is a unique and consistent pattern of combustion. Most cases are fatal fires. Occasionally you find someone like my patient who only "smoked."

The combustion pattern is that all the fat and all the bones (note bones contain marrow which has a lot of fat in it) are reduced to ash. All other organs are left largely intact, perhaps just a little bit charred. If it happens indoors, there is a pink grease stain on the ceiling, and I'm guessing that's just burned fat. And any flammable material that is either in contact with the body or immediately within millimetres of the body, material that should have caught on fire if this were a normal fire, did not catch on fire.

So I started thinking about this. Again, what would Occam's Razor say about this? It's almost certain there's only one thing going on here and that it's mast cell disease. So how can mast cell disease possibly produce spontaneous human combustion?

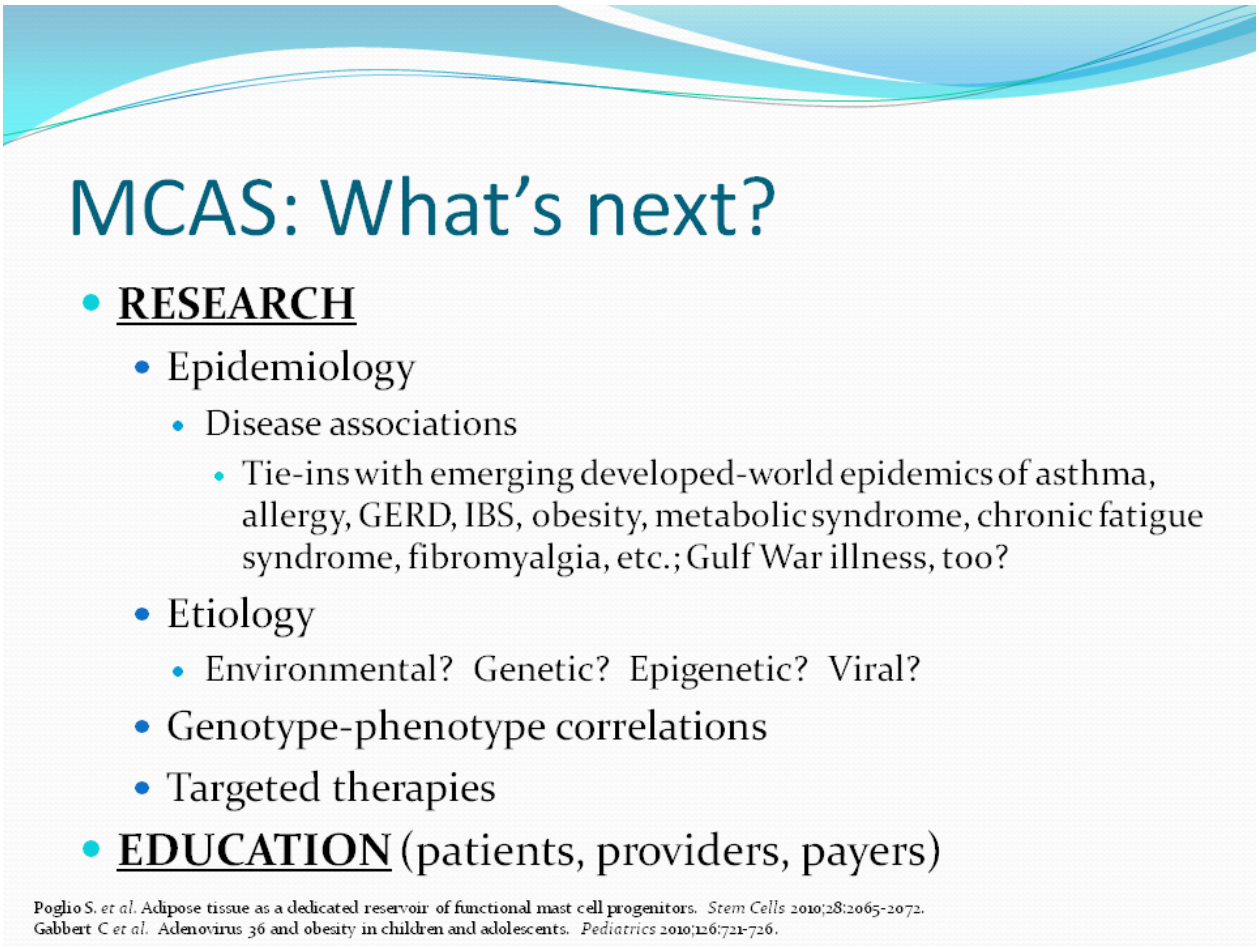
I started doing some reading and calculating. This is entirely hypothetical. I haven't presented this anywhere before. But here is a possibility, that's all I'm saying, a possibility.

The average trim adult has 50 billion adipose cells. The average obese adult has 70 billion adipose cells. Adipose tissue is a known mast cell reservoir. There are about 1-2,000 mitochondria per adult animal cell, and it is the mitochondria that are the source of heat in your body. Now, we also know that norepinephrine is a known mast cell mediator. It is produced by the mast cell.

In what is normally a very carefully regulated process (as you might imagine), norepinephrine affects a cell's mitochondrial UCP1 protein. This is a switch in the mitochondria that ordinarily channels energy released from fatty acid oxidation of the mitochondria into ATP production. But in the presence of norepinephrine, UCP1 is switched to a different state such that the energy being released by fatty acid oxidation is just released as heat.

So is it possible that an unregulated flood of norepinephrine (or some other mediator which serves to switch UCP1) from a mast cell flare in the adipose tissue could drive UCP1-mediated heat release so much that the fat escalates to ignition temperature (which is less than you might think, a little bit below the boiling point of water). The average cell is capable of producing 5 nanowatts of heat under ordinary circumstances, so if I'm doing the math right, the human body can produce 250 watts of heat per second. Of course, when you escalate temperature of the body to that degree, you very quickly get brain shutdown, the patient dies, and there's no way the mast cells are continuing to release the norepinephrine, but by that point it doesn't matter anymore. The fire has started and it will continue until all the fuel – that is, all the fat – is consumed. This is all hypothetical. I have not a clue how spontaneous combustion actually happens because it's never been observed, and never will be observed, under controlled conditions. However, I've become a big believer in Occam's Razor, and if mast cell disease is causing all the rest of this patient's problems, it seems most likely it's causing his smoking, too. The only question becomes "How?"

[Slide 121: MCAS: What's next?]



We obviously need to do a whole lot more research. We need to better understand what diseases that presently are idiopathic are actually just different flavours, different presentations of mast cell disease. I'm trying to get a study going with the U.S. Veterans Affairs Dept. The U.S. sent 700,000 military servicemen and servicewomen to the Gulf War in the early 1990s. Three hundred thousand came back with serious, chronic multi-system illness (many of them different from one another) we've taken to calling Gulf War Syndome or Illness. Twenty years' and a billion dollars' worth of research later, we still don't have a clue why they are sick. However, in my work at the VA in Charleston, I've seen a number of these Gulf War Syndrome patients, and I feel their clinical profile just reeks of mast cell disease. I've actually been able to do partial workups in two of them so far, and they're both positive for mast cell disease. So I'd like to rigorously study this because if we get answers to what's making 300,000 people sick…well, let me ask you this, as this segues greatly into the scale of MCAS – how many patients have CML? What's the incidence of CML? Oh, sorry, I'm guessing you wouldn't know the U.S. figures, but it's about 8,000 people per year.

Dr. Trinkaus: In Canada, it's 800 cases per year.

Dr. Afrin: The total U.S. population of CML patients is about 50,000. So if Gulf War Syndrome turns out to be due to MCAS, this finding would instantly dramatically expand the scale of chronic myeloproliferative disease in the U.S. even if one doesn't believe that MCAS might cause all the other illnesses I previously mentioned I suspect it causes. I don't have proof of this MCAS/Gulf-War-Syndrome connection yet, and the studies will be challenging, but from what I've been seeing the past three years, I believe I have good reason to suspect that mast cell activation syndrome is a whole lot more common than any of the diseases for which the tyrosine kinase inhibitors are being targeted. Time will tell.

We also need to better understand the etiology and epidemiology of MCAS. There clearly are many families out there with multiple members of the family with mast cell activation syndrome, but often different members of the same family have very different presentations. What we think is going on is that although the KIT mutations and the other mast cell regulatory protein mutations themselves are not being inherited, there is some sort of a susceptibility factor (possibly an epigenetic factor) that's being inherited, and that factor is interacting with unknown environmental factors – more commonly early in life rather than later – and the interaction of the trigger with the susceptibility factor is then what leads to the mutations that we know are there in MCAS. But different triggers interacting with the susceptibility factor may lead to the different mutations, explaining how different members of the same family get different flavours of mast cell activation syndrome.

We need to get to the point where we are routinely sequencing at least KIT, and preferably the entire genome, and that's not as farfetched as you might think. We're probably about 5-10 years away from this. Once we know the mutations, then we can start correlating the mutations with the pattern of abnormal mediators that are present in the individual patient, then correlate that with symptoms, correlate that with response to treatment, and we'll finally get to a point – we're easily talking 15-20 years in development here –where the disease gets suspected, it gets diagnosed, you get a sequence, and based on the sequence you can predict which treatments are most likely to help that patient.

We clearly also need better education about mast cell disease for medical professionals of all stripes.

I apologize for running late. This is basically everything I've learned about this since I first began to recognize it in 2008. Thank you.

Remainder of audio is discussion amongst doctors about questions, tests to run, symptom presentations, etc.