The learning objectives of my talk today are to understand the differential diagnosis and management of leukocytoclastic vasculitis, or LCV, to understanding the differential diagnosis and management of central nervous system vasculitis and to understand the differential of a positive ANCA test including potential causes of false positivity.

So first I'll just give a very general overview of the vasculitides and then I’m going to go over two cases which were very interesting. The first was a consultation in the hospital for LCV and a question of systemic vasculitis, and the second was a case of questionable primary CNS vasculitis and for each of these cases I'm going to be giving you just a few sort of pointed take home teaching points and then we'll just end with a short conclusion.

So what is vasculitis? It's a group of chronic inflammatory diseases of unknown etiology where the immune mediated injury is targeted at the blood vessel wall itself and in the blood vessel there is a constant dialogue between the vessel and the immune system. And in this disorder the immune system is targeting the blood vessels in any organ or tissue and it's often a multisystem disease and can manifest differently in any one individual.

So the vasculitides are one group of diseases but obviously each vasculitis is not the same as the other. There are distinct age, sex and ethnicity groups of patients that get affected, serologies are helpful in diagnosing certain vasculitides but even then is limited, there is different organ system
involvements and different vascular preferences in terms of type and size of blood vessels that get involved.

So here you can see that group of systemic vasculitides is very large and we won't have time to cover them all today, just briefly you can see they are broken down into large vessel, medium vessel, small vessel vasculitides and also some with no predominant vessel size. Today's talk we are going to be focusing first on leukocytoclastic vasculitis or LCV and this is really actually an entity that can be seen in any of these small vessel vasculitides. We will also focus on the ANCA-associated vasculitides which include granulomatosis with polyangiitis or GPA, this used to be called Wegener's and we've pretty much gone away from using that name because this was a Nazi doctor actually, microscopic polyangiitis or MPA and also eosinophilic granulomatosis with polyangiitis or EGPA and that used to be called Churg-Strauss syndrome and again we are getting away from using that term, also because they were Nazi doctors. And then CNS vasculitis we are going to also focus on. It's a rare vasculitis, no predominant vessel size but very important as far as mimickers.

So this is the Chapel Hill Nomenclature Classification that's been described and like I say it's broken down largely by the size of blood vessel that gets involved, so that's the first thing you should try to differentiate in a patient if you think they have vasculitis what size blood vessel do you think it's involving? So large vessel vasculitis includes the Takayasu Arteritis and Giant Cell Arteritis, medium vessel vasculitis is predominantly Polyarteritis Nodosa or PAN and Kawasaki Disease which is primarily a pediatric disease. And then you get into the small vessel vasculitides and even
in this schematic you can see that they do overlap in terms of some of the small vessel vasculitides do also involve some medium size vessels, so it's not a hard cutoff but we have the ANCA-Associated Vasculitides here which we've talked about, then there is also Anti-GBM disease which is Goodpasture's, also immune complex mediated small vessel vasculitides including cryo, Henoch-Schönlein purpura also IgA vasculitis and the hypocomplementemic urticarial vasculitis also called anti-C1q vasculitis.

So here are some features, clinical features that generally correlate with the size of blood vessel involvement. So if you see a patient and they come in with skin changes including purpura, vesicles or bullae, urticaria or cutaneous necrosis or if they are presenting with alveolar hemorrhage or glomerulonephritis, acute kidney injury or scleritis or episcleritis you really should be thinking a small vessel vasculitis.

Medium size vessel vasculitis in the skin you will see things like nodules, ulcers, fixed livedo reticularis, and digital gangrene. Also mononeuritis multiplex, I'd say this entity can occur in both small or medium vessel vasculitis and also microaneurysms especially of the renal arteries in PAN.

And then large vessel vasculitis patients will primarily be presenting with extremity claudication symptoms, you may detect it incidentally by a blood pressure asymmetry between the two sides, absent pulses between the two sides. I always like to check radial pulses simultaneously because that's the only way you can actually pickup an asymmetry between the two sides. You want to listen
for bruits especially in the carotid and subclavian areas, aortic aneurysms and stenoses and then in all of these vasculitides you'll have the patient complaining of really nonspecific constitutional symptoms including fevers, unexplained weight loss, malaise, myalgias, arthralgias. Okay so we are going to enter our cases today. These are really interesting cases.

The first one - they were both seen at the UPMC hospitals and the first case was a 49-year-old white male with a recent history of deep vein thrombosis and history of complicated gastric bypass who presented to the emergency dept. at the outside hospital with severe hypotension, acute kidney injury with a creatinine bump to 4.3 and clinical sepsis. 2 to 3 days prior to admission he had presented to the ED for a rash of his lower extremities and was treated with Keflex for presumed cellulitis. However the cellulitis worsened despite the Keflex treatment. And in the ED he was diagnosed with sepsis, disseminated intravascular coagulation and pneumonia and admitted for further management.

On a CT of the chest he was found to have cavitary lesions in his right lung, a large one at the right lung base with an air-fluid level and a small one was noted at the right upper lobe. And of note, the skin biopsy of the outside hospital of this "cellulitis" actually showed leukocytoclastic vasculitis or LCV. The rheumatoid factor was very elevated and he had a high positive ANA of 1-320. And obviously with all of these different findings rheumatology was promptly consulted.

Now he did have an echo, a transthoracic echo and that had shown no vegetation to suggest endocarditis, and in the outside hospital he had already had some significant labs including a severe
leukocytosis with a left shift, there was no eosinophilia. He did have a few red cells on the UA but nothing really severe. He'd already had some workup for rheumatologic things including a normal ACE level, a normal complements, hepatitis B and C antibodies were negative, he had an elevated ferritin but not in the range of adult onset Still's disease and Jo-1 and Scl-70 antibody were negative.

So when he arrived here we performed some more labs of course and he was noted to have normal renal function. He did have severe hypoalbuminemia, elevated inflammatory markers. Again we found a high positive rheumatoid factor, a high positive ANA, ANCA was actually negative, the CCP or cyclic citrullinated protein antibody which is a test for rheumatoid arthritis was negative. SSA/SSB, Sm, RNP were all negative. He had an elevated IgG level, HIV was negative and sputum cultures just showed normal respiratory flora, neg. AFB stains and just a little bit of yeast.

So on review of systems he was complaining of fatigue and just an occasional mild cough productive of scant clear sputum, no hemoptysis. He was so noting the weight loss from - he had like a poor appetite ever since his gastric bypass but otherwise he denied the rest of the review of systems.

And going into his past medical history and surgical history it's important to note that after his gastric bypass in '01 he did have multiple complications including removal of a portion of his stomach in 2009 and a perforated ulcer in 2005. He'd had this chronic anemia since the gastric bypass requiring almost monthly infusions to the point he even had a chest wall port placed in 2009.
He had known osteoarthritis status post bilateral knee replacements and you can see his other comorbidities there.

Social history, he was a lifetime nonsmoker, no alcohol or drug use, he denies any recent sick contacts, travel or incarceration. Family history was noncontributory. You can see his medication list there, these of course were just in-hospital. The allergies actually significant for Penicillin which caused a rash, but this rash was different than the rash he had from - at the time that he was treated with the Keflex.

And then on exam he had 2+ edema in the bilateral upper and lower extremities, he had no synovitis or deformities on complete joint exam. He had palpable purpuric confluent skin rash and lesions on the bilateral lower extremities, worse on the left than the right and then also a focal purpura lesion on his right thumb and skin desquamation of the bilateral thumbs.

So this is a picture of the leukocytoclastic vasculitis, it wasn't - this is not actually this exact patient but his skin did look very similar to this, a lot of purpuric lesions, sort of confluent mostly on the distal lower extremities. Some of them were even you now coalescing almost becoming bullas and like I said the skin biopsy we already knew that the outside hospital was showing LCV.

So he was started on broad spectrum antibiotics, Vancomycin, Meropenem, Azithromycin. His white count actually was trending down over the first few days in the hospital to 10.9 but he was still
complaining, I mean these painful purpuric skin lesions were very poorly healing, he was complaining of generalized pain, still had that little occasional cough so we were performing more workup in hospital. Because of his high positive rheumatoid factor we did get radiographs of his hands and there were no erosive or productive arthropathy changes seen.

And this was an imaging that really helped move things along. We performed a repeat ET chest in our hospital and compared it to the outside CT chest from 8 days earlier and it actually showed this increase in the size of the complex right pleura and parenchyma collection, concerning for an abscess. And it also was made note that given the proximity to the esophageal jejunal anastomosis and adjacent gas locules anastomotic breakdown or a fistula at the location was possible.

So obviously we consulted thoracic surgery promptly. He had a chest tube and pigtail catheter placed for drainage, a repeat CT chest 6 days later showed significant reduction in this right lung fluid collection and so the chest tube and pigtail catheter were removed. He did complete a total of 3 weeks of IV Meropenem, an EGD and barium swallow was negative for entero-pleural fistula but a stricture was found and so the etiology of this abscess in his lung was thought to be likely from chronic aspiration in the setting of an esophageal stricture. And very interestingly his palpable purpura resolved soon after the chest tube drainage of the right lung abscess, where it you know wasn't improving at all until that point.
So I just want to make a few teaching points here. The first point of this case I think is the LCV may be a manifestation not only of systemic small vessel vasculitis but also infection. So LCV is often also termed hypersensitivity vasculitis or hypersensitivity angiitis, it's really a histopathologic term that denotes a small vessel vasculitis and is characterized histologically by leukocytoclasis which just means vascular damage caused by nuclear debris from infiltrating neutrophils. And it classically presents as palpable purpura and less commonly as urticarial plaques, vesicles, bullae or pustules. The differential diagnosis of LCV includes medications, underlying infection, collagen vascular disorders or malignancy; however approximately half the cases are idiopathic.

From a rheumatologic standpoint there is many things in the collagen vascular disorder that that we were of course entertaining in our consultation. But especially the small vessel vasculitides including the ANCA-associated kind, rheumatoid vasculitis since he had that high positive rheumatoid factor, also connective tissue disease, associated vasculitides like Lupus and Sjögren's.

So LCV may be localized to the skin or may be associated with systemic involvement. Internal disease most often manifests in the joints, GI tract and the kidneys and in the absence of systemic involvement the prognosis of LCV is actually excellent, 90% resolve in weeks to months. And cases localized to the skin alone should be treated conservatively. They are usually responding very well just to removal of the offending agent or drug, treatment of the underlying infection or malignancy, etc. And you really should avoid the use of systemic steroids and immunosuppressive agents unless it's a chronic or recurrent disease, and sometimes doing nothing is harder you know as a
rheumatologist coming in consulting, it's almost harder to withhold and not give steroids empirically but you have to keep this in mind in particular with LCV.

The second case point I want to make is that not all cavitary lung lesions in the setting of LCV equals systemic vasculitis. Although cavitary lung nodules are seen in both rheumatoid arthritis and AAV these diagnoses require careful attention to the entire clinical picture. The patient lacked the synovitis or joint deformities of rheumatoid arthritis and his ANCA was negative and yet no history at all of sinusitis or any acute kidney injury. The differential for cavitary lung lesions also includes infectious causes of course like abscess in this case, also tuberculosis and nocardia, etc. Also malignancy and thromboembolic sources too. And the third and final case point I want to make from this case is that false positive rheumatoid factor and/or ANA may also be just due to infections. Just like vasculitis the diagnosis of RA, lupus and other connective tissue diseases require the presence of appropriate clinical manifestations, not just positive serologies. The patient denied arthralgias besides minor knee pain from his known osteoarthritis, the CCP which is a more specific antibody for rheumatoid arthritis than the rheumatoid factor was negative. And he denies any photosensitivity, Reynaud's or other lupus specific symptoms.

Okay, moving on to the second case. She was a 22 year old white female with history of Crohn's disease since age 9 and had recently started Adalimumab which is also called HUMARA 3 or 4 weeks ago and she also had a history of iron B12 deficiency anemia and primary sclerosing cholangitis.
She was admitted with a 3 week history of dysphagia, odynophagia, mental status changes, blurry vision and gait difficulties. In the emergency dept. she was noted to have neurologic deficits and a MRI brain was performed that showed multiple supra and infratentorial lesions consistent with thrombotic versus embolic events. A CT of the head and neck showed diffuse mild irregularity of both the anterior and posterior circulation raises the possibility of vasculitis and so obviously rheumatology was promptly consulted for this.

On review of systems she was complaining of some mental clouding, it wasn't quite at her baseline but it had improved some. She still had the generalized left grade and right sided weakness, some blurry vision still, she also complained of some constipation and urinary hesitancy. As far as musculoskeletal symptoms she just had some knee pain with her Crohn's flairs in the past, nothing acute recently and she was no longer complaining of the dysphagia or odynophagia, no burning paresthesias or ulcers, hearing deficits, asthma, allergies, sinusitis, the rest of the review of systems was negative.

A little bit about her Crohn's disease history, she was on Mesalamine as a maintenance and then she had been on Azathioprine since age 18 but that was discontinued in March and she had recently started Adalimumab just one week prior to the symptom onset. And she would get like maybe 1 or 2 flares of her Crohn's disease per year which would be treated with just sort of short courses of
steroids. She also had this PSC and that was diagnosed on ERCP and she was about to start Ursodiol soon and she was on supplements for her iron and B12 deficiency anemia.

Social history, she was a nonsmoker, no alcohol or drug use, a college student, no pregnancies. Her sister was actually a medical student. Her family history was significant for father with Guillain Barre syndrome but was otherwise noncontributory. You can see her medication list here.

On exam the pertinence included focal muscle weakness, 4/5 weakness on the left upper extremity, 3/5 weakness on the left lower extremity. She did have dysmetria with her hand movements on finger to nose testing, left worse than the right. She had upgoing Babinskis bilaterally. No sinus tenderness or oral or nasal ulcers and no synovitis on complete joint exam.

On laboratory workup here at UPMC she had a severe anemia and then of interest she had this eosinophilia of unclear etiology, it was all the way up 30% by the second day. She also had elevating inflammatory markers and elevated troponin also of unclear etiology. She was found to have a positive c-ANCA and she also had positive antihistone antibodies, a mildly low C4, some - a couple antiphospholipid antibodies including a weak positive lupus anticoagulant. It was an isolated hexagonal lipid neutralization test and just a beta 2 GP 1 IgG. On CSF analysis it was normal, the viral studies on the CSF were negative and then interestingly when she had a real cerebral angiogram as opposed to just the MRA you know that was read as normal with no evidence of vasculopathy at
all. She also had an echo that showed normal EF and there were no intracardiac embolic sources found there.

So we did pursue a brain biopsy and that was negative for vasculitis for you know CNS vasculitis and she also underwent a cardiac MRI that showed a diffuse subendocardial enhancement that was consistent with subendocardial fibrosis and no intracardiac thrombi. And this was suggestive of endomyocarditis. So at this point hematology was consulted and suspicion was raised for a hyper-eosinophilic-like syndrome, possibly drug induced from Adalimumab given her eosinophilia, multiple strokes like a hypercoagulable state from this and the endomyocarditis and it all coming on sort of right after she had started Adalimumab. And she was treated with high dose steroids with significant improvement.

So I just want to make a couple of teaching points from this case. There were a lot of sort of issues when you know going through it when we first got consulted and throughout the course. The first thing is that false positive ANCAs may be due to a history of inflammatory bowel disease, primary sclerosing cholangitis and/or drugs. The positive predictive value of a c-ANCA is only 45 to 50% and this does increase in the right clinical context if you combine the indirect amino fluorescents method of testing, in other words the c versus p-ANCA combined with the ELIZA test which is specifically the proteinase 3, PR3 or myeloperoxidase MPO. So if you have a positive c-ANCA and a positive PR3 or a positive p-ANCA, a positive MPO that actually increases the specificity to 99%, but again this is with the right clinical context. Specifically the C-ANCA PR3 is quite sensitive for
GPA and then the p-ANCA MPO is quite sensitive for MPA, but this patient denied any other symptoms of ANCA associated vasculitis. She had no history of chronic sinusitis, asthma, allergies, nasal crusting, epistaxis or renal disease, and these are all really important questions to ask. And I actually think this patient's ANCA was more likely a false positive from her history of PSC, Crohn's and/or the Adalimumab actually.

So these - some other conditions associated with ANCA, asbestosis, pulmonary TB, pneumonia, cystic fibrosis, different sort of fungal or paracytic infections, endocarditis, other autoimmune diseases and I mentioned the IBD, actually about 75 to 80% of patients with active ulcerative colitis or PSC will have a positive ANCA. It's usually a p-ANCA actually unlike in her case, Lupus of Sjögren's. Drug-wise you can see a false positive ANCA from cocaine/levamisole is probably one of the most common things when people abuse those drugs, also PTU, Hydralazine, TNF inhibitors like the Adalimumab and Minocycline and then of course malignancies or neuroplasms can also cause false positive ANCA. And like I mentioned GPA although PR3 is more commonly seen in GPA and MPO is more commonly seen in MPA you actually can see a fair number of patients just with pulmonary TB or pneumonia having these antibodies. And I also wanted to point out that in Churg-Strauss syndrome only 40% of the patients actually have and it's usually a p-ANCA or MPO.

So the second case point I want to make is that although CNS vasculitis is one cause of multiple strokes in multiple territories at a young age it is still a very rare condition. And other differential
diagnoses including hypercoagulable states need to be kept in mind. So the first thing with this case I mean there was a discrepancy between her MRA of the brain and neck and her cerebral angiogram where the MRA was raising the question but the cerebral angiogram which is a much more sensitive type of test than the MRA actually was read as completely normal. And then plus the CSF findings were normal in her case which also went against CNS vasculitis. So when in doubt pursue brain biopsy which we did in her case. And the other thing is you know if the MRI brain looks thromboembolic be very thorough in your hypercoagulable workup. I mean we are not sure how much of those antiphospholipid antibodies also came into play but they probably were contributing as well to her hypercoagulable state.

Okay, so I just want to review a little bit about CNS vasculitis, also called primary angiitis of the CNS or PACNS. This is a vasculitis that affects small and/or medium sized intracranial cerebral blood vessels and it classically presents as multiple strokes in multiple territories at a young or middle age. A little bit more commonly in men, 2 to 1 male to female ratio. The mean age 42 and inflammation of the CNS vessels causes stenoses and/or occlusions leading to tissue ischemia. Symptoms may also include decreased cognition, headache or seizures. The SED rate and CRP are actually typically normal in primary CNS vasculitis and CSF analysis is crucial because it can be abnormal in 80 to 90% of patients and although there is no specific abnormality it's usually high protein that's seen.
On diagnosis basically cerebral angiography is the main method and it classically reveals beading which is alternating ectasia and stenoses. There is no single angiographic feature that's like 100% diagnostic. A negative angiogram still cannot exclude the diagnosis, usually an MRA is done first because that's the noninvasive test but the resolution is inadequate to image the very small cerebral blood vessels. And then you also have to beware of false positive MRAs as in this case because that's just sort of due to artifact. And then the brain biopsy is still the gold standard, however the false negative rate can be up to 25% in autopsy cases. So the preferred site of a brain biopsy is a radiologically abnormal area.

I just want to mention the differential diagnosis of primary CNS vasculitis includes this reversible cerebral vasoconstriction syndrome, hypercoagulable states, amyloid angiopathy, systemic vasculitis involving the brain which includes you know a number of different rheumatologic diseases, infection, atherosclerosis or cerebral emboli including from cardiac sources and intravascular lymphoma.

A little note about RCVNS, this typically presents as a severe headache in the setting of a postpartum of migraine history or Pseudoephedrine use and the CSF analysis is typically normal and you will see reversible, completely reversible angiographic findings within days to weeks. So sometimes if you have questions of this you can just repeat that angiogram in a couple of weeks. If you have a high suspicion for this you should consider a calcium channel blocker for immediate treatment.
Okay, and then the third and final case point of this case is that eosinophilia and a positive ANCA does not equal Churg-Strauss syndrome. So Churg-Strauss syndrome or EGPA is typically defined by history of having severe asthma, which this patient lacked, significant eosinophilia of greater than 10% like in her case should be further investigated. EGPA is less commonly associated with positive ANCA than the other ANCA associated vasculitides and this eosinophilia that came into this case you know actually is not common associated with primary CNS vasculitis so that kind of threw us onto another workup.

So here you can see out of the 1998 ACR criteria for EGPA, she really only had this one, the blood eosinophilia count greater than 10%, she didn't have any of these other - the asthma, the neurologic involvement, transient pulmonary infiltrates, sinus abnormalities or histologic proof of vasculitis. If you have 4 or more of these that actually has a high sensitivity and specificity of EGPA and I think I've mentioned a couple of times now that you know it has a weaker association with p-ANCA.

And just finally a little bit about hypereosinophilic syndrome, this is defined as eosinophilia with associated organ dysfunction without an apparent cause such as paracytic disease or allergies. And obviously paracytic disease worldwide is still more common than this entity so it is important to remember that on your differential for eosinophilia. However eosinophilic myocarditis like this patient had is a major morbidity of this syndrome, it is typically found on echo and/or cardiac MRI just like she had, cerebral or thromboemboli may occur and cause strokes and TIAs, multiple infarcts
in the watershed zones and just like how she presented can cause encephalopathy with behavioral changes, confusion, ataxia and memory loss. It may also cause other thrombotic complications including digital gangrene, Reynaud's and intracranial sinus thrombosis and it may be difficult to distinguish from Churg-Strauss syndrome or EGPA, especially because steroids are helpful for both conditions so really tissue biopsy is the most helpful to exclude vasculitis.

So in final conclusions LCV is a nonspecific histopathologic term for a small vessel vasculitis of the skin. LCV may be seen in infection, malignancy, drug hypersensitivity or systemic small vessel vasculitides. False positive ANCs may be due to inflammatory bowel disease, primary sclerosing cholangitis, drugs, infections, cystic fibrosis, malignancy or other connective tissue diseases. Primary CNS vasculitis is characterized by multiple strokes in multiple territories at a young age but so are hypercoagulable states. And finally eosinophilia and ANCA positivity in the absence of an asthma history should really entail further investigation.