Metformin-Induced Giant Cell Arteritis: An Uncommon Case of Drug-Induced Vasculitis

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Background

- The most common form of vasculitis is secondary to drug use, wherein a pharmaceutical agent causes the inflammation of blood vessels. The diagnosis of drug-induced vasculitis is often made by assessing the synchronicity between the initiation of the offending pharmaceutical agent and the clinical presentation of a vasculitis. The most common drug-induced vasculitis takes the form of ANCA-associated vasculitis, causing inflammation of small- and medium-sized vessels. The primary presentation is often associated with cutaneous lesions, also seen in the lungs, liver, central nervous system, and kidneys. Patients have also reported myalgias and arthralgias. The most common medications associated with drug-induced vasculitis are various antibiotics, anti-tumor necrosis factor-α agents, and psychoactive agents (1). Among the various miscellaneous drugs, metformin is rarely listed as a medication associated with drug-induced vasculitis, nor is there current mention of involvement with the development of medium- and large-sized vasculitis. We present a rare case of metformin-induced giant cell arteritis (GCA), also known as temporal arteritis.

Case

- **Chief complaint:** 81-year-old Asian female presents with new-onset headache following the initiation of metformin
- **HPI:** She began metformin 2 weeks prior to the development of her symptoms. She self-discontinued metformin and her symptoms resolved. When she resumed her metformin, the pain recurred resulting in an emergency room visit.
- **Past medical history:** Hypertension, osteoarthritis, and a carrier of Hepatitis B
- **Medications:** Amlodipine and metformin
- **Review of systems:** Positive acute right neck pain with pain to the right frontal area of her head
- **Physical Exam:** A painful palpable mass with palpation of the right side of her head, and soft bruit in carotid artery

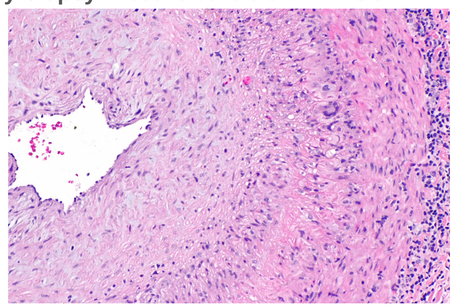
Results

Labs

Lab	Result	Lab	Result
ESR (mm/hr)	15	dsDNA (IU/ml)	16
Hgb A1c	7.2%	ANA	Negative
Alk phos (IU/L)	51	α1/α2 globulins	Positive
C-reactive protein (mg/L)	42.5	IgA, IgG, IgM	Within normal limits

Imaging: Head CT, head MRA, and bilateral carotid US all unremarkable

Temporal artery biopsy: Results consistent with GCA



- Figure 1. Micrograph of giant cell arteritis. H&E stain (including red blood cells, artery lumen, giant cell, internal elastic lamina, and smooth muscle of tunica media). This file is licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license.

Discussion

- Currently, the pathogenesis of drug-induced vasculitis has not been formally established and is still poorly understood, but data suggests an autoimmune component may be a part of its multifactorial mechanism. The two forms of drug-associated vasculitis are the immune complex and the ANCA-associated forms. The main distinction between drug-associated vasculitis and idiopathic vasculitis is that discontinuing the drug would correct the autoimmune reaction causing the drug reaction (2). GCA is found most commonly in female adults older than 50 years old, with the mean onset age of 75.
- Drugs have been listed as a potential initial insult to the endothelium in GCA along with infections, trauma, or autoantigens. This initial insult then activates dendritic cells that are present in the adventitia. The resulting immune cascade leads to the activation of macrophages. Systemic inflammation occurs with the release of metalloproteinase and oxygen free radicals alongside IL-1 and IL-6. This is marked by endothelial damage as the internal elastic lamina is disrupted. Nitric oxide is secreted in the intima leading to the formation of syncytia, giving it the characteristic “giant cells” (3).

Discussion, cont.

- A small number of case presentations have implicated metformin as the cause of a drug-induced vasculitis. Often these patients will present with cutaneous manifestations including ulcerated sores or purpura. When metformin was withdrawn, no new lesions develop and the present lesions would begin to heal (4). In one case presentation, metformin was linked to the presentation of purpuric papules in the lower region of a patient’s body beginning from her lower abdomen extending to her legs. A biopsy taken of the lesions revealed perivascular polymorphonuclear infiltrates in the small dermal vessels which was consistent with leukocytoclastic vasculitis. Upon discontinuation of metformin a rapid improvement of the skin eruption was noted. When metformin was reintroduced, an identical eruption occurred (5).
- Per the Naranjo Algorithm and ADR Probability Scale, it is likely that there is a causal relationship between the initiation of metformin and development of GCA in this patient (6). A limitation of this case study is the presence of the patient’s chronic hepatitis B diagnosis. Polyartertitis nodosa (PAN) which is a vasculitis that affects the small and medium-sized blood vessels has been linked to hepatitis B. Leukocytoclastic vasculitis secondary to HBV infection is rare, with only a few reported cases. It is also less likely in this patient as her IgA, IgG, and IgM levels were within normal limits (7).

Conclusion

- Given the temporal relationship of the development of GCA and the initiation and re-introduction of metformin in this patient, we are convinced that metformin was the cause for the development of her vasculitis. As metformin is a widely-used drug and is first line for treatment of type 2 diabetes mellitus, it is important for clinicians to be aware of the link between this medication and the various ways drug-induced vasculitis can manifest during its use.

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