Case Presentation

Disguised discoloration: Minocycline-induced pigmented cardiac valves

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Abstract

Tetracyclines are used for a variety of dermatologic conditions, and a known side effect of this therapy is hyperpigmentation in multiple tissues throughout the body. We present the case of a 66-year-old man who underwent aortic valve replacement and was found to have discoloration of the aortic valve leaflets associated with his chronic use of minocycline for rosacea. Minocycline-induced pigmentation of cardiac valves is a documented, although uncommon, phenomenon. There is no evidence linking valve pigmentation to functional valve defects. This case highlights an infrequent manifestation of minocycline-induced pigmentation.

Introduction

Minocycline, a tetracycline derivative, is commonly used to treat acne and rosacea.[1,2] It has been reported to cause pigmentation in various tissues, including the skin, thyroid gland, and cardiac valves.[1] Minocycline-induced cardiac valve pigmentation has been described only a few times in the cardiothoracic literature.[1,3] Cardiovascular pigmentation is generally associated with long-term minocycline use, with 1 study reporting aortic valve pigmentation after more than 30 years of therapy.[3] The present case describes a patient on minocycline therapy for approximately 5 years for rosacea who was found to have discolored aortic leaflets during valve replacement surgery.

Case Synopsis

A 66-year-old man underwent planned aortic valve replacement for symptomatic aortic stenosis. He had been taking minocycline 50 mg daily for approximately 5 years, prescribed for rosacea by his primary care physician. During surgery, the aortic valve leaflets, annulus, endocardium, and papillary muscles were noted to have black and gray discoloration (**Figure 1**). The aortic valve leaflets and annulus were heavily calcified, as expected. No other areas of minocycline-induced pigmentation were noted on physical examination. The patient had no history of ochronosis and was not taking any other medications commonly associated with drug-induced pigmentation.

Histologic examination of the aortic valve demonstrated nodular fibrosis with extensive calcification and focal myxoid degeneration (**Figure 2**). Histiocytes containing brown pigment were present within areas of fibrosis. The brown pigment stained positively with both iron and Fontana-Masson (melanin) histochemical stains (**Figure 3** and **Figure 4**). The aortic valve replacement was otherwise uneventful. Postoperatively, the patient elected to discontinue minocycline and was instructed to follow up with his outpatient provider for ongoing management of rosacea.

Case Discussion

Minocycline-induced hyperpigmentation of the cardiac valves has been rarely reported in the literature.[1,3,4] Hyperpigmentation of various tissues is a well-known side effect of tetracycline use. When this discoloration appears on the skin, patients may choose to discontinue the medication for cosmetic reasons. Although cutaneous hyperpigmentation can be distressing aesthetically, it is a benign side effect that does not require discontinuation unless the patient prefers to stop therapy.

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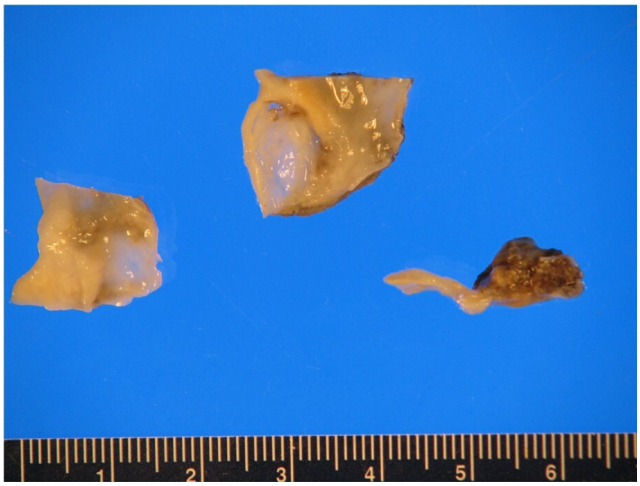

Figure 1. *Gross photograph of the aortic valve showing fibrosis, calcification, and brown-black discoloration.*

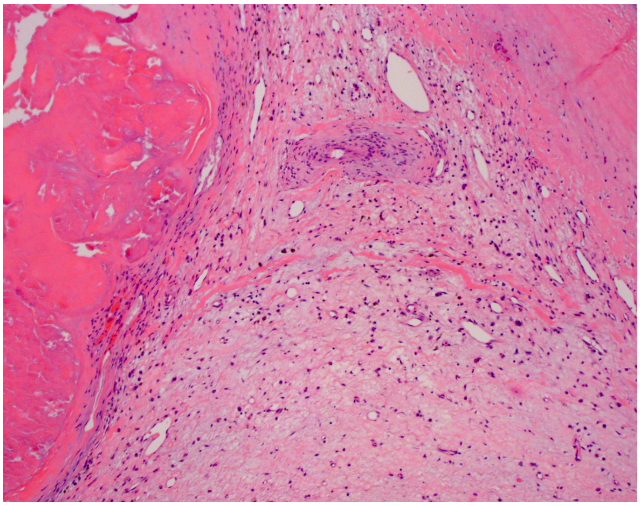

Figure 2. *Calcification and fibrosis with sparse lymphomononuclear inflammation (hematoxylin-eosin, original magnification ×20).*

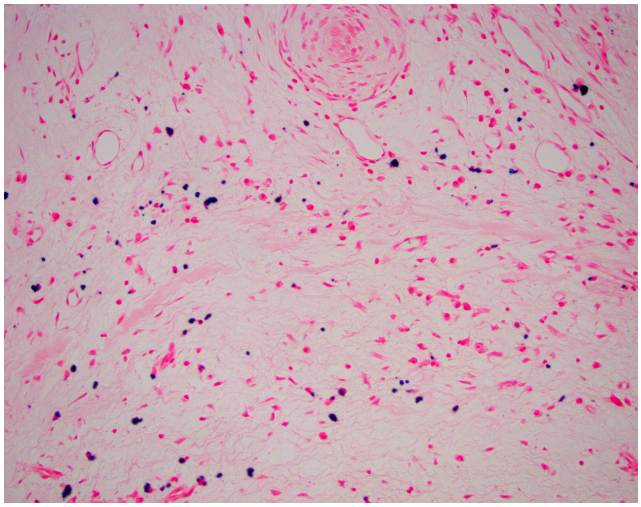

Figure 3. *Positive staining in pigmented macrophages (Perls' Prussian blue [iron], original magnification ×200).*

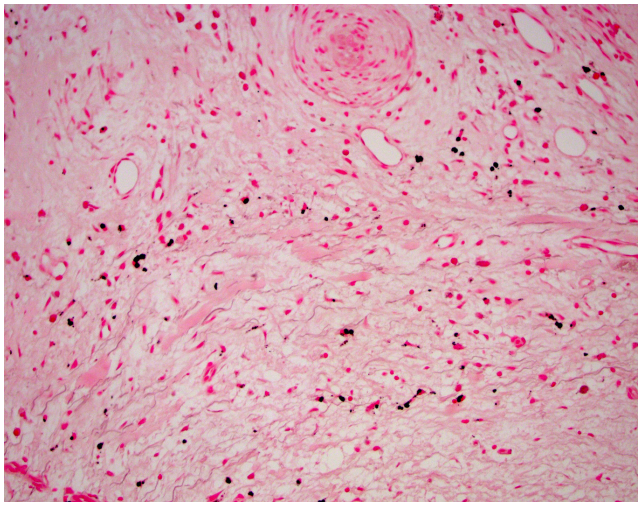

Figure 4. *Positive staining in pigmented macrophages (Fontana-Masson [melanin], original magnification ×200).*

To our knowledge, there have been no reports in the literature of pigmentation causing functional defects in cardiac valves; therefore, it is unlikely that the discoloration of the valves contributed to the development of aortic valve calcification in our patient. One report described minocycline-induced hyperpigmentation of the aorta and coronary arteries, which was initially concerning for aortic dissection.[4] Although the discoloration was ultimately benign, this highlights the need to maintain a high index of suspicion when encountering unusual pigmentation.

When discoloration of connective tissue is discovered, a broad differential diagnosis should be considered, including alkaptonuria, Addison disease, heavy metal deposition, and medication-induced pigmentation. A thorough history, including medication use and potential exposures, along with physical examination is necessary to determine the cause. Biopsy of affected tissues can aid in distinguishing between potential etiologies.

Cutaneous hyperpigmentation from long-term minocycline use is classified into 4 types.[5] Type I presents as blue-black pigmentation in areas of previous inflammation or scarring; the classic presentation is blue-black macules on the face in areas of acne scarring. Type II occurs in previously normal skin, particularly the lower legs. Types I and II are histopathologically characterized by brown-black pigment granules in macrophages that stain with both Perls' Prussian blue (iron) and Fontana-Masson (melanin) stains. Type III presents as diffuse muddy brown pigmentation in a photodistributed pattern, with increased pigment in basal epidermal keratinocytes and dermal melanophages, staining only with Fontana-Masson. Type IV has been described as blue-gray pigmentation within scars, similar to type I, but occurring on the back.[6] It differs from type I in that the pigment stains only with Fontana-Masson and not with Perls' Prussian blue.

Cardiac valves removed for stenosis typically demonstrate a combination of degenerative changes, including

fibrosis, myxoid degeneration, and calcification. In the present case, the pigmentation was associated with fibrosis/scar in the valve tissue and stained positively with both iron and Fontana-Masson stains. Several mechanisms have been proposed to explain minocycline-induced cardiovascular pigmentation, including stimulation of melanocyte activity, generation of pigmented metabolites through drug oxidation, and formation of iron-binding complexes.[4] Based on the staining characteristics, valvular pigmentation may result from a combination of these processes.

According to the literature, most cases of cardiac valve hyperpigmentation are identified years after the initiation of minocycline therapy.[3,4] This suggests that valve discoloration develops more gradually compared with hyperpigmentation at other sites, such as oral mucosa, nails, and sclera, which may appear within a few weeks of starting therapy.[4]

Conclusion

This case highlights an uncommon presentation of minocycline-induced black and gray pigmentation of the aortic valve leaflets, annulus, endocardium, and papillary muscles. To date, there is no evidence linking minocycline-induced pigmentation to morbidity or mortality; however, physicians should be aware of this potential side effect and remain vigilant.

Potential conflicts of interest

The authors declare no conflicts of interest.

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