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Re: Still about Francesco de' Medici's poisoning (1587)

Dear Editors,

This is the reply to the Letter to the Editor in response to my article in an issue of the American Journal of Medicine.

Thank you for your kindness.

Sincerely,

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## The malaria of Francesco I de' Medici (1587): a confirmed diagnosis

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The finding of a document with a description of the conditions of Francesco I in the last moments of his life is of particular interest, as it allows to further clarify the causes of the Grand Duke's death.

In this document the symptoms presented by Francesco are petechiae, fever and swollen neck. Prof. Lippi concludes that this account "supports the conclusion of poisoning" of a previous work,<sup>1</sup> because "skin eruption (such as petechiae), fever and swelling are symptoms of acute arsenic poisoning".

In acute arsenic poisoning skin rash is described, but only in the form of flushing erythema or maculopapular eruption.<sup>2</sup> These findings are totally different from petechiae, historically associated with infectious diseases such as epidemic typhus, which the 16<sup>th</sup> century physicians could certainly distinguish. On the contrary, these dermatological manifestations are described among the symptoms of malaria, and are mainly seen with *falciparum* species.<sup>3</sup> The skin lesions consist in petechiae, which are small (1-2 mm) red or purple spots on the body and are caused by minor haemorrhagies.<sup>4</sup> The incidence of malaria manifesting with purpura (diffused petechiae) is reported in the range 1.33% to 25.6%.<sup>5</sup>

The second symptom mentioned in the document is fever, which is never described in acute arsenic poisoning and is instead typical of malaria.<sup>3</sup>

With regard to the "swollen neck", although it is a very generic symptom that is not helpful in the diagnosis, it is well-known that swollen neck lymph nodes are a common sign of many infections, not of intoxication.

Finally, as already discussed in the comments to the original paper,<sup>1</sup> there are no evidences of arsenic poisoning of Francesco I, simply because the toxicological analyses were carried out on very questionable soft tissue remains,<sup>6</sup> that most likely cannot be attributed to Francesco.

On the contrary, ancient *Plasmodium falciparum* proteins were really detected in the skeletal remains of the Grand Duke, demonstrating without any doubt that he was affected by *falciparum* malaria at the time of his death.<sup>7</sup>

I am grateful to Prof. Lippi for having found the Vatican document, which further supports the diagnosis of severe, acute malaria as the cause of death of Francesco I de' Medici.

## References

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