Gout in Duke Federico of Montefeltro (1422-1482): a new pearl of the Italian Renaissance

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Abstract

The article examines the truthfulness of historical accounts claiming that Renaissance Duke Federico of Montefeltro (1422–1482) suffered from gout. By direct paleopathological assessment of the skeletal remains and by the philological investigation of historical and documental sources, primarily a 1461 handwritten letter by the Duke himself to his personal physician, a description of the symptoms and Renaissance therapy is offered and a final diagnosis of gout is formulated. The Duke's handwritten letter offers a rare testimony of ancient clinical self-diagnostics and Renaissance living-experience of gout. Moreover, the article also shows how an alliance between historical, documental and paleopathological methods can greatly increase the precision of retrospective diagnoses, thus helping to shed clearer light onto the antiquity and evolution of diseases.

Key words

gout, paleopathology, rheumatology, Federico of Montefeltro, Renaissance

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Received on May 8, 2017; accepted in revised form on December 22, 2017.

Competing interests: none declared.

Introduction

In medieval medicine gout was used as a general word encompassing several nosological entities (1-2). The term, adopted since the 13th century, derives from the Latin *gutta* (*i.e.* drop), and reflects the idea that this condition was caused by an imbalance of a humour entering the affected joint, thus causing pain and inflammation. The distinction between gout and other forms of rheumatism was only introduced in the 17th century (3-4).

While the historico-medical records allow us to retrospectively identify the presence of gout in the past, it is often difficult to make a precise diagnosis of this rheumatic form of arthritis exclusively on the basis of osteoarchaeological material; the cases of gout are in fact rare and, above all, the most important aspects of the diagnostic process, *i.e.* the anamnesis or the patient's history, are generally missing. It should also be remarked that, while in many instances we have an indirect description of the disease suffered by prominent historical characters, we very rarely have any documentation in which these important figures provide an account of their problems, depicting for example the signs and symptoms by which they are affected. In this paper we report on the detailed self-written description of an acute attack of arthritis experienced by Federico of Montefeltro, one of the eminent representatives of the Italian Renaissance, and compare it with an accurate analysis of his medical history and of his skeletal remains through the lens of palaeopathology.

Archaeological, taphonomic and historical background

Federico of Montefeltro (1422-1482), Duke of Urbino, is still remembered as one of the chief warlords of the Italian Renaissance. His profile portrait painted by the renowned artist Piero della Francesca (1416/1417-1492), exhibited in the Uffizi Museum in Florence (Fig. 1), shows the sewn contours of his nose and the *gravitas*-filled expression of a victorious commander and acclaimed patron of the arts. Aged sixty, he set out for his last military campaign in the plains near Ferrara (Emilia-Romagna region, northern Italy), where on 10 September 1482 he was struck by fever and died probably of an infectious disease like malaria, contracted in the marshy theatre of war (5-6). His corpse was taken to Urbino (Marche Region, central Italy) for the celebration of the funeral rites (5-6). After embalming, the Duke's body was placed in a wooden coffin hung on the wall, to the right of the main altar in the church of San Bernardino. It remained there at least until 1620, when two cenotaphs, still present, were built and positioned against the walls, while the body was placed in a burial chamber under the floor. The corpse was exhumed twice throughout history: in 1824 and, more recently, in 1938; on both occasions the clothes and skeletal remains were found in a rather poor state of preservation. The last exhumation in 2000 confirmed the very bad conservation status of his skeletal remains. In particular, the bones were reduced to only a few hardly recognisable fragments, as a result of an extremely damp microclimate and post-depositional interventions by tomb raiders (7).

While historical research is still investigating the Duke's complex political career, the medical conditions that af-

Fig. 1. Duke Federico of Montefeltro in the "Double portrait of the Dukes of Urbino" (1465–1472) by Piero della Francesca, Uffizi Gallery, Florence, Italy [inventory no. 1890] (by permission of the Uffizi Gallery Director. Not to be copied or duplicated by any means).

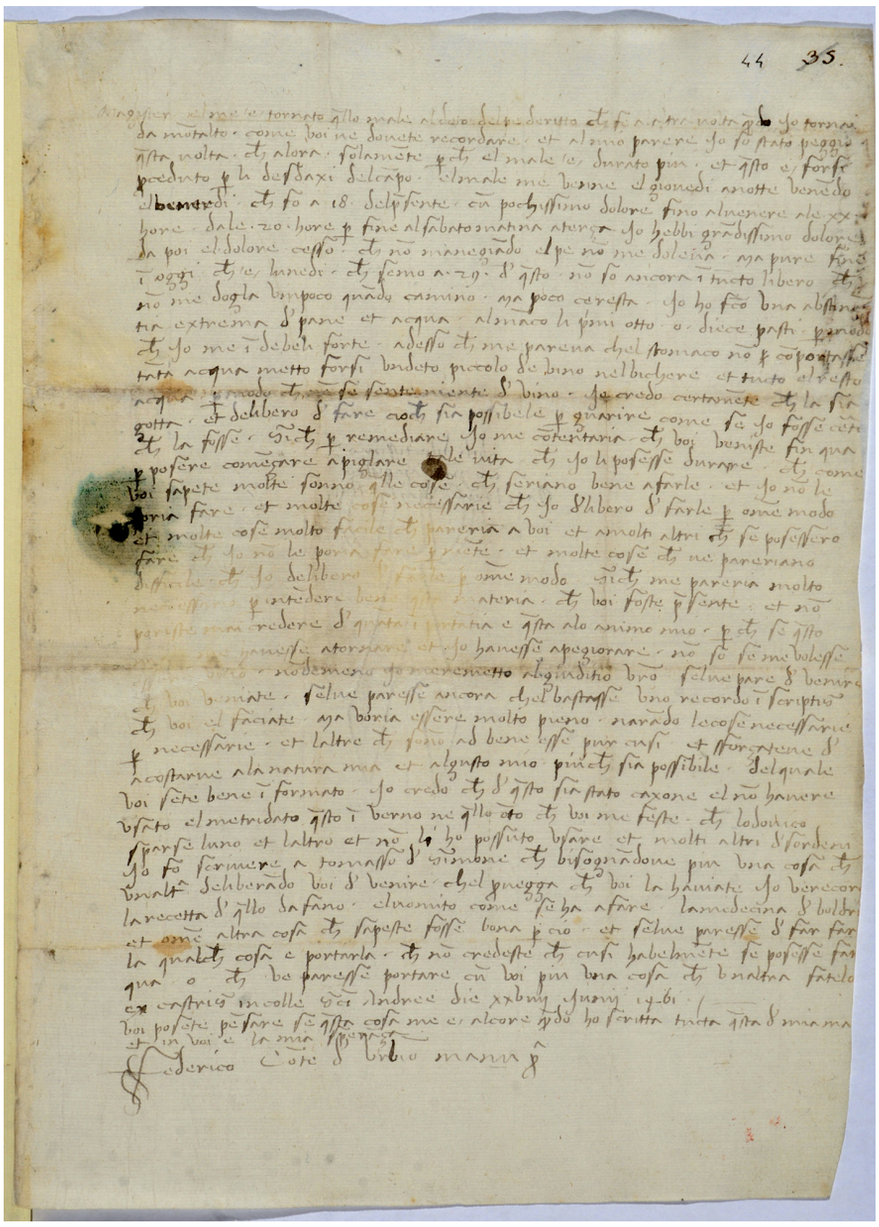

Fig. 2. Federico of Montefeltro's handwritten letter to his physician Battiferro of Mercatello [inventory number: Archivio di Stato di Firenze, Ducato di Urbino, Serie I, Filza 104, carta 44 r-v] (by permission of the Italian Ministry of Cultural Heritage and Tourism. Not to be copied or duplicated by any means).

fected him throughout his existence have basically remained neglected. With the exception of a robust discussion on the mystery of the strange morphology of his nose, in which the osseous nasal bridge seemed to be missing (8), the ailments (including the exact cause of his death) that affected him are still open to discussion. Although his alleged medical conditions are still under scrutiny, historians have long suggested that he might have suffered from gout which, in combination with a dislocation of his left foot that occurred on November 27, 1471 in San Marino, greatly affected his locomotion and capacity to take an active part on the battle-field (5-6).

However, the most important source for the reconstruction of the Duke's disease is the handwritten letter (Fig. 2) that Federico of Montefeltro himself wrote to his physician Battiferro of Mercatello on 29 June 1461, [inventory number: Archivio di Stato di Firenze, Ducato di Urbino, serie I, Filza 104, carta 44 r-v]: "Master, the pain in the toe of the right foot that I had the last time I returned from Montalto has come on again [*me è tornato quello male al dito del pe deritto che fe alaltra volta*], as you certainly remember, and in my opinion this time I feel worse than I did last time [*jo so stato peggio questa volta che alora*], just because the pain has lasted longer and has probably increased for the hardships of the camp [*solamente perché el male è durato più · et questo è forse proceduto per li desdaxi del campo*]".

Federico informs his physician that the pain in his right toe has returned; he assigns the greater crudeness of the pain to the hardships suffered during the military campaign, and then describes the typical symptoms of gout attacks in detail: "The pain came on the night between Thursday and Friday, on day 18 of this month, with very little pain [*cum pochissimo dolore*] until Friday at 20 hours; from 20 hours until the third hour of Saturday morning I had tremendous pain, then the pain ceased because [*jo hebbi grandissimo dolore da poi el dolore cessò*], since I was not eating, my foot did not hurt [*che non manegiando el pe non me doleva*], but until now, which is Monday, the 29th of the month, I have not been entirely free from this pain, because it hurts a little when I walk, but it does not last long [*non so ancora in tucto libero che non mi dogla umpoco quando camino · ma poco ce resta*]. I have been on an extreme diet of bread and water […]".

Having recognised the symptoms, Federico self-diagnosed gout: "I think it must be gout [*jo credo certamente che la sia gotta*], and I will do what I can to cure it as if I were sure it was. […]. This use of the term "gout", as seen above, was however quite broad, meaning rheumatic ailments in general. The Duke adds some comments on several interesting pharmacological aspects and attributes the recrudescence of gout to the fact that the previous winter he had not used the medicines that Battiferro had prescribed: "I think the cause is not to have used the mithridate this winter nor that ointment that you prepared me [*jo credo che di questo sia stato caxone el non havere usato el metridato questo inverno ne quello onto che voi me feste*]".

Federico is worried about his health and he repeatedly invites his physician Battiferro to reach him at his military camp: "I will be satisfied if you come here [*io mi contentaria che voi veniste fin qua*]. […] If it seems appropriate to come, do come "[*sel ve pare di venire che voi veniate*]. You can well see how much I care about this matter for I have written all this by my own hand and my hope lies in you [*voi posete pensare se questa cosa me è alcore quando ho scritta tucta questa di mia mano et in voi è la mia speranza*].

Paleopathology

The majority of the remains found in Federico's tomb were not preserved well enough to allow a clear-cut retrospective diagnosis of any major diseases. However, the still well preserved osteological remnant, which could serve this purpose, is the first metatarsal bone of the Duke's right foot (Fig. 3).

The medial side of the metatarsal head exhibits a circumscribed periarticular lytic lesion with excavated appearance and projecting margins delimiting the surface of the lacuna (Fig. 4). The dimensions of the lesion are 17x13 mm, although one of the margins of the lesser axis evidently suffered some post-depositional damage. New reactive spongy bone within the lesion and sclerosis around the margins have been macroscopically observed and confirmed by radiographic and CT images (Figs. 5 and 6). The lesion appears to be the result of a chronic inflammatory process with predominantly destructive but also reparative phenomena. No birefringent urate crystals have been observed by polarised-light microscopy analysis.

Fig. 3. Federico of Montefeltro's fully skeletonized first right metatarsal bone showing clear signs of erosion at the medial head.

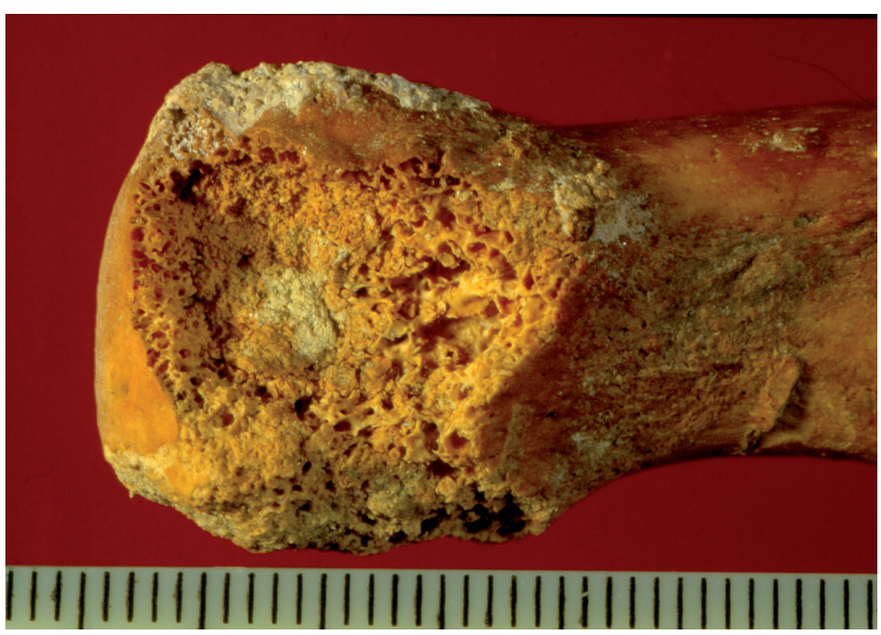

Fig. 4. Detail of the medial aspect of Federico of Montefeltro's first metatarsal bone showing an erosion pattern suggestive typical of gout.

Discussion

From a paleopathological point of view, the diagnosis of gout is based on the localisation and features of typical bone lesions. Inflammation and pressure by para-articular *tophi* produce erosions on the articular surface, at its margins or even at some distance from the joint. These scooped-out defects are asymmetrical and, although penetrating into the bone, they fail to make their way into the marrow cavity, prevented from accessing it only by a thin layer of bone. A proliferative reaction can produce projections similar to a hook at the margins of the lesion, known as Martel's hook sign (9); sclerotic margins around the lesion and overhanging edges are commonly observed features at x-ray analysis (10-11). Although gout is expected to be found in osteoarchaeological remains especially from the Modern Age, when this inflammatory disorder was a common condition, the disease seems to be underestimated in paleopathology (9-15). Despite a confident diagnosis that can result from the skeletal features, the signs of the disease probably remain unobserved, as groundwater usually removes urate crystal making it difficult to recognise the aetiology of lytic lesions.

In addition to the paleopathological diagnosis, the handwritten letter of Federico of Montefeltro is a rare case of medical history of a 15th century celebrity. The violence of the distressing attacks

Fig. 5. X-ray image of the first right metatarsal bone in antero-posterior projection, clearly highlighting the lesion on the medial side.

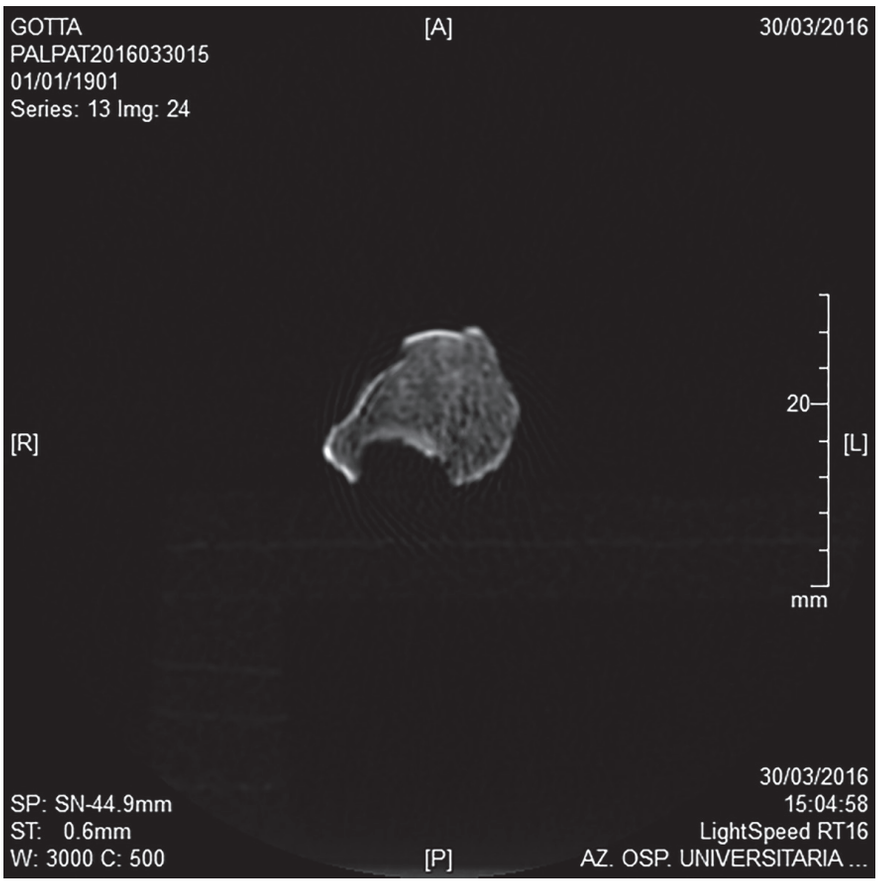

Fig. 6. CT scan image of the right first metatarsal bone better highlighting the circumscribed periarticular lytic lesion and its excavated aspect with sclerosis around the margins.

and the development of pain as described by the patient Federico are typical of gout, and the letter attests a previous similar episode in the same foot.

In this specific instance, he explains the increased violence of the painful attacks with the hardships suffered in the military camp: in those days of June 1461 Federico was in the Latium region as commander of the papal army against some lords who had rebelled to Pope Pio II (2), and the dehydration phenomena are likely to have facilitated the onset of the attack.

We know that in 60% of cases a genetic cause is responsible for variations in uric acid levels and for the establishment of the pathological condition of gout (16); however, the diet of the Renaissance aristocratic classes was unbalanced, with an immoderate use of red meat, especially wild game, that may have favoured the onset of gout and other diseases (17-19).

In addition, the difficulty of expelling uric acid is likely to have been enhanced by the abundance of lead that was ingested through food. This metal, used as a food preservative, was an important component of pewter tableware, and was also massively present in the glaze of ceramic pots (20). In our case, the skeletal remains of Federico were kept in a coffin covered with slabs of lead, and therefore it would have been useless to analyse the lead contained in the bones of the Duke, certainly present on account of diagenetic phenomena.

Therefore, the pharmacological data and the information emerging from the text of the letter concerning the psychological status of the Duke, as sick patient-subject, are extremely precious. Firstly, the Duke confesses that he has not followed the prescriptions of the physician and thus attributes the return of gout to his own fault, as often happens in contemporary clinical experience when patients forget to take specific antipurine drugs. The letter mentions the use of mithridate, an ancient medical potion containing a great number of additives and chemical principles, and thought to have been invented by the Hellenistic king Mithradates VI Eupator of Pontus 135–63 BC (21). Already in the days of the Roman physician Aulus Celsus (c. 25 BC-c. 50 AD) mithridate was said to contain: *Acorus calamus* (sweet flag), *Hypericum*, *Iris germanica (German iris)*, *Elettaria cardamomum* (true cardamom), *Pimpinella anisum* (anise*)*, *Valeriana officinalis (*valerian*)*, *Gentiana* (gentian), *Lolium temulentum* (darnel ryegrass)*, Piper longum* (long pepper), *Papaver rhoeas* (common poppy)*, Saxifraga, Petroselinum crispum* (parsley), *Cinnamomun verum* (true cinnamon), *Zingiber* (ginger) and many others elements, such as *castoreum,* resin of *Liquidambar orientalis,* frankincense, myrr and honey.

Ginger (Lat. Zingiber) in particular was considered to have some beneficial effect on rheumatic ailments (22-23). It has not been possible to determine whether the mithridatium used by Federico contained ginger, whether it could have any real effect on his health, or whether it was another substance, contained in mithridatium or in different medical preparations (such as the above-mentioned ointment), which had a positive effect on the Duke.

The letter written by Federico witnesses a patient-physician relationship dating back to over 500 years ago, and shows the real intimate nature of the duke, a patient suffering from a most painful condition. The letter starkly contrasts with other more formal letters and dispatches, in which he was trying to appear powerful and in full control of the political and military activities. This clearly turns the first-hand documentation into an even more precious and reliable source of information. Although the exact composition of the mithridatium and ointment administered to Federico of Montefeltro has not been determined, the beneficial effects of his disease may have been produced by the combination of pharmacologically-induced modification of the symptomatology of his disease and the placebo effect represented by the evidently well-functioning patient-physician interaction.

Conclusion

Federico of Montefeltro represents a unique case in the history of medicine and paleopathology, where it is possible to link the life experiences of "the patient" to osteoarchaeological finds. The voice of the patient reveals and reflects the humanity of the duke, seen as a man and not only as a clever politician or famous warlord.

From a scientific point of view, the present study achieves important results. Firstly, it morphologically and radiologically proves that the gout suggested by historical sources actually affected the Duke and that it was most likely gout, as conceived by present day medicine. Secondly, it clearly demonstrates that a virtuous combination of osteology-based paleopathology and source-based paleopathology (*i.e.* paleopathography) is not only possible, but also increases diagnostic accuracy in ancient human remains (24), greatly reducing the risk of misdiagnosis and anachronism in retrospective pathological reassessments.

Acknowledgements

The authors wish to thank Prof. Gino Fornaciari and Prof. Stefano Bombardieri (University of Pisa) for his revision of the text, Davide Giustini (Division of Diagnostic and Interventional Radiology, Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa) for technical assistance and Francesco Martelli (Resp. settore archivi medicei e Scuola di archivistica dell'Archivio di Stato di Firenze) for kindly allowing the study and provinding them with an image of Federico of Montefeltro's letter to the physician Battiferro. The authors also thank the Arpa Foundation and the Mäxi Foundation for supporting this research, Mr Michael E. Habicht (Institute of Evolutionary Medicine, University of Zurich, Zurich, Switzerland; School of Humanities and Creative Arts, Department of Archaeology, Flinders University, Adelaide, Australia) for his precious suggestions on the conducted research. Finally, the authors express their gratitude to Mr Owen Burke (Aylesbury, UK) for his careful linguistic revision of the manuscript and to Prof. Giovanni Spani (The College of the Holy Cross, Worcester, MA, USA) for his paleographic and philological insights.

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