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A medieval case of digitalis poisoning: the sudden death of Cangrande della Scala, lord of verona (1291–1329)

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ABSTRACT

The natural mummy of Cangrande della Scala was exhumed from its tomb in the church of Santa Maria Antiqua in Verona and was submitted to a multidisciplinary study, that included archaeological, palaeopathological, palynological, toxicological and historical investigation. The body of Cangrande, still wearing his precious clothes, was in a good state of preservation. Palynological analyses demonstrated the presence of pollen grains of *Digitalis* sp./foxglove in the rectum content, along with *Matricaria chamomilla*/chamomille and *Morus nigra*/black mulberry. Toxicological analyses showed toxic concentrations of digoxin and digitoxin, two *Digitalis* glycosides, in the liver and faeces samples. Both palynological and toxicological data suggest an intoxication through the oral administration of an infusion or decoction of leaves and flowers of *Digitalis*.

Cangrande died on July 22 1329, four day after his triumphal entrance in the city of Treviso. The sudden death was preceded by vomit and diarrhoea with fever that, according to written documents, he had contracted a few days before by "drinking from a polluted spring". The gastrointestinal symptoms manifested by Cangrande in his last hours of life are compatible with the early phase of *Digitalis* intoxication and the hypothesis of poisoning is mentioned by some local historical sources. The palaeopathological analyses confirm a *Digitalis* poisoning. The most likely hypothesis on the causes of death is that of a deliberate administration of a lethal amount of *Digitalis*. Although several cases of poisoning through the use of organic substances are known from historical sources, no other direct evidences are documented in the palaeopathological literature.

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1. Introduction

Cangrande della Scala (1291–1329) is the most celebrated member of the Scaligeri dynasty, which ruled Verona from 1277 to 1387 (Varanini, 1988; Spangenberg, 1993).

Leading patron of the poet Dante Alighieri, who composed a letter (Epistola XIII) in honour of his host in Verona (Branca, 1907), Cangrande was a great warrior and an important autocrat of his time. After the death of his brother Alboino he became the sole ruler of Verona in 1311, at the age of twenty. Cangrande was regarded as the leader of the Ghibelline party in Northern Italy,

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bringing the city of Vicenza under his control (1314). After several years of intermittent and brutal conflicts he took possession of Padua (1328) and Treviso (1329).

On 18 July 1329 the entrance of Cangrande into the city of Treviso represented the crowning achievement of his long struggle to submit the entire region of Veneto (Northern Italy). However, his triumph was marred by the fact that he had become seriously ill as a result of vomit and diarrhoea, which he had contracted a few days before by “drinking from a polluted spring”, according to contemporary accounts (Varanini, 2004). Cangrande died on the morning of July 22.

The body of Cangrande was temporarily housed in the church of Santa Maria Antiqua in Verona, but it then appears to have been moved twice, first to a marble tomb in the churchyard and secondly to the monumental marble tomb over the church entrance, above which there is an equestrian statue of Cangrande in tournament armour (Fornaciari, 2004; Napione, 2006) (Fig. 1).

In February 2004 the tomb of Cangrande was opened to allow a multidisciplinary study of the corpse, which included archaeological, palaeopathological, palynological, toxicological and historical investigation. The natural mummy, still wearing its precious clothes, appeared in good state of preservation (Napione, 2006).

The aim of this paper was to investigate the causes of Cangrande's death, taking also into consideration that rumours of poisoning are reported by traditional chronicles (Varanini, 2004).

2. Materials and methods

2.1. Palaeopathological study

The mummy of Cangrande (Fig. 2) was submitted to autopsy (Fig. 3a), performed through a circular opening of the abdomen, from the sternum to the pubis, which allowed to reach the abdominal and thoracic cavities (Fornaciari, 2004, 2006). The viscera appeared to be collapsed on the posterior wall and were identified according to their topographical position. Macroscopic, radiological and histological studies were performed. The latter included rehydration with Sandison solution (Sandison, 1955), routine paraffin-embedding and standard haematoxylin-eosin and Van Gieson's staining procedures.

Fig. 1. The equestrian statue of Cangrande (Castelvecchio Museum, Verona).

2.2. Palynological analysis

Samples for palynological analyses were taken from two internal regions of Cangrande's mummy, the left hemi-abdomen (colon) and the rectum content (faeces). The analyses were carried out applying an already tested analytical approach (Giuffra et al., 2011). The method includes the following phases: addition of a tablet of *Lycopodium* spores re-suspended in HC1 10% for the calculation of pollen concentration (=number of pollen grains/gram); treatment with acetic acid to dehydrate the preparation; Erdtman acetolysis; addition of 40% of HF without pre-heating for 24 h; washings in distilled water; addition of ethanol; desiccation in thermostatic oven; preparation of glycerine jelly-fixed slides. The observation of the samples was performed at 1000× light microscope magnification (ocular 10× and objective 100×) with the help of keys, atlases and a reference pollen collection. In particular, the identification of the *Digitalis* pollen was obtained by using a manual (Moore et al., 1991), whereas that of *Digitalis* cf. *purpurea* was based on the comparison with the laboratory collection of the authors.

The pollen terminology is based on Berglund and Ralska-Jasiewiczowa (1986). The botanic terminology follows Pignatti (1982).

2.3. Toxicological analysis

Toxicological analyses were performed on different samples taken from the mummy of Cangrande to detect any traces of poisons or toxic substances or to find evidences of any possible pharmacological treatments, which could explain his rapid death. In particular, the toxicological analyses were carried out on a sample of hair (100 mg) from the head vertex, two samples of rectum content (approximately 5 g each), and two liver samples (approximately 5 g each), which have been collected during the autopsy.

The extracts of the hair sample, of one faeces sample, and of one liver sample underwent screening toxicological analyses by using CE and HPLC-MS methods.

The CE analyses were performed on a P/ACE-MDQ capillary electropherograph equipped with a diode-array detector operating at 214 nm (Beckman Coulter, Fullerton, CA, USA). Separations were carried out at 25 °C in an uncoated fused-silica capillary (Composite Metal Service Worcester, UK), with an internal diameter of 50 μm and a total length of 60 cm, using a buffer composed of 100 mM phosphate (pH 2.38) (Hudson et al., 1995).

The HPLC-MS analyses were performed on a 1100 HPLC coupled with a MSD-ion trap mass spectrometer, model SL (Agilent Technologies, Palo Alto, CA) using a Zorbax Eclipse XDB (2.1 × 150 mm, 5 μm particle size, Agilent Technologies) with gradient elution from 5% to 95% of solvent B lasting 20 min (solvent A: formic acid 0.1%; solvent B: methanol). The spray voltage was set at 4 kV and the skimmer at 40 V. For peak identification, the ion trap mass spectrometer was set to perform MS^2 on the molecular ion of the selected compounds, using helium as collision gas.

The results of screening analyses were confirmed by using a 1100 HPLC coupled with a quadrupole Time of Flight Mass Spectrometry (Q-TOF MS) Ultima (Waters MS Technologies, Manchester, UK). The separation was performed using a Synergi Hydro column

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