

# Severe atherosclerosis in the natural mummy of Girolamo Macchi (1648–1734), “major writer” of Santa Maria della Scala Hospital in Siena (Italy)



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## HIGHLIGHTS

- In the crypt of S. Maria della Scala Hospital (Siena, Italy) a 17th century natural mummy was found; it was Girolamo Macchi.
- A complete study, including macroscopic, radiological, isotopic and histological analyses, was performed on the mummy.
- The circulatory system, like the lumbar aorta, showed atherosclerosis, with calcifications stenosing the lumen of the vessels.
- The diagnosis was confirmed by imaging techniques (3D Cone Beam Scan) and by histology.
- Atherosclerosis in ancient subjects indicates that the disease could be an inherent component of human ageing.

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## ABSTRACT

**Background and aims:** A small crypt in the Santissima Annunziata Church of Santa Maria della Scala Hospital in Siena (Italy) contained three well-preserved mummies, two of which, dated back to the 15th–16th century, were identified as Salimbene Capacci (1433–1497), Rector of the Hospital, and his wife, Margherita Sozzini (?–1511). The third mummy, dressed in clothes of the 17th century, was not initially identified.

**Methods:** Accurate bibliographical, taphonomic and anthropological studies allowed the identification of the mummy of Girolamo Macchi, who lived between 1648 and 1734 and worked as “major writer”, an accountant, for the Hospital. He was present when the corpses of the Rector and his wife were discovered in 1678 and, impressed by this finding, wanted to be buried in the same chapel after his death, which occurred at the age of 86. A complete study, including macroscopic, radiological, isotopic and histological analyses, was performed on the natural mummy of Girolamo.

**Results:** Macroscopic investigation showed a large inguinoscrotal hernia and a good preservation of the internal organs. The circulatory system revealed severe atherosclerosis, with multiple calcifications stenosing the lumen of the vessels, in particular of the lumbar aorta and the iliac arteries. The diagnosis was confirmed by imaging techniques (3D Cone Beam Scan) and by histology.

**Conclusions:** This case confirms that atherosclerosis is also a disease of ancient times. The presence of atherosclerosis in pre-contemporary individuals could suggest that the disease may not only be uniquely characteristic of a specific diet or lifestyle, but it could be also an inherent component of human ageing.

## 1. Introduction

Atherosclerosis, disease in which the lumen of an artery narrows up to occlusion, caused by buildup of plaque composed of fatty material on the inner walls, is one of the most common pathologies among the

developed countries and every year thousands of people die by the complications of the atherosclerotic disease (in Central Europe: 201 man and 117 women per 100,000 inhabitants per year [1]).

Atherosclerosis is a multifactorial disease, with involvement of modifiable risk factors (tobacco, obesity, hypertension, diabetes,

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dyslipidemia) and non-modifiable risk factors (sex, advanced age, genetic predisposition, family history) [2].

The first study that hypothesized the correlation between atherosclerotic obstruction and myocardial infarction dated to 1912 [3], even though the description of the plaques by some anatomists goes back well before this date. Among the first to describe atherosclerosis was Leonardo da Vinci (1452–1519), who stated that ‘vessels in the elderly restrict the transit of blood through thickening of the tunics’ [4].

Due to its connection with dietary habits, the disease had been considered peculiar of the modern sedentary and well-nourished society, with diet characterized by a rich intake of meat, sugar and fat. However, the presence of atherosclerosis in mummies of different temporal horizons and different geographic contexts suggests the potential that other risk factors or causes could result in atherosclerosis, in addition to a diet rich in meat, sugar and fat, but numerous paleopathological studies have now disowned this point of view. A high incidence of atherosclerosis in mummies belonging to different temporal horizons and different geographic contexts has been demonstrated [5,6]. Moreover, recent studies of large samples of individuals seem to demonstrate that in the past the disease occurred with an incidence similar to that of current times [7]. In fact, in addition to wrong dietary habits, another possible risk factor for the onset of atherosclerosis is the chronic inflammatory state by frequent infections [8], certainly more recurrent in the past than in the modern population.

Should we therefore reassess our considerations regarding the ‘epidemic’ of atherosclerosis of the contemporary age? Can we still find out something we do not know?

Indeed, the presence of atherosclerosis in pre-contemporary individuals could suggest that the disease may be an inherent component of human ageing and not a characteristic of a specific diet or lifestyle [9].

Paleopathology can contribute, with new cases, to formulate further questions and new answers.

## 2. Materials and methods

The mummy of Girolamo Macchi was laying in an anthropoid coffin without cover, close to the artificial mummified bodies of Salimbene Capacci (1433–1497) and Margherita Sozzini (1511†) [10]. Inside the coffin, there was a lead tube containing two manuscript pages, left on September 8th, 1948 to remember the exhumation of that year.

The mummy, in dorsal decubitus, was dressed in the white hood and clothes typical of the lay confreres, a white dress (gown), with a rosary in his hands and the feet tied up with a strip. On the mummy, four devotional medallions were also discovered.

The mummy was subject to complete paleopathological investigation. In 1999, the macroscopic examination, the autopsy, sampling of the specimens and imaging reconstructions with CT scanner were performed. More recently, the samples underwent 3D Cone Beam Scan, histological and immunohistochemical studies, and stable isotopic investigations for paleonutrition.

### 2.1. Macroscopy

Macroscopical examinations took place in the laboratory of the Division of Paleopathology in Pisa. To avoid contaminations the body was positioned on a disinfected autopsy table covered by sterile surgical drapes. The autopsy was performed with access in the back in order to minimize the impact on the body and to facilitate the future restoration, as suggested by Aufderheide [11]. Paleopathologists wore sterile surgical coats, sterile latex gloves, sterile masks, headdresses and overshoes. The mummified specimens (abdominal aorta with the bifurcation of common iliac arteries, inguino-scrotal hernia) were immediately kept and sealed in sterile containers, reducing the possibility of subsequent contamination.

### 2.2. Imaging

The imaging studies were performed at the Division of Diagnostic and Interventional Radiology of the University of Pisa using a third generation CT scanner GE Sytec, Kv 120, MA 100, slice thickness 10 mm, field of view 42 cm.

Cone-Beam computed tomography (CBCT) images were also acquired. CBCT is a widely used three-dimensional diagnostic technique, which allows extremely accurate imaging of hard tissues. The strength of this method lies in the possibility of obtaining images of high diagnostic quality, due to good spatial resolution [12]. The primary characteristic of CBCT is the cone-shaped X-ray beam localized at the source of radiation and the base on the detector, which allows diminishing image distortion and exposure time. The shape of the beam influences effectively the patterns of image acquisition. In Multi-Slice CT (MSCT), the fan-shaped beam allows the acquisition of the volume through a rotating gantry wherein the patient moves at constant speed. Therefore, the images are obtained as a set of multiple axial sections. In CBCT, the dataset is acquired as an entire volume during a single gantry revolution. The advantage is the possibility to reconstruct the volume in any plane with high fidelity.

The use of CBCT is highly recommended for hard-mineralized tissues (e.g. in the dental field); in fact, for its technical characteristics it does not allow proper imaging of soft tissues, for which the MSCT is therefore preferable.

CBCT can be effectively applied to the study of ancient human remains due to the high diagnostic value, providing detailed information of the bony structures [13] without the risk of damaging the specimen.

In our study, two fragments of the aortic and iliac artery were studied to assess the possible presence of intimal calcifications associated with atherosclerosis, relying on the high spatial resolution of the technique.

Planmeca Promax® 3D Classic (Planmeca Group, Helsinki, Finland) CBCT equipment was employed. We performed a single acquisition of the two specimens with the following parameters: 8 cm FOV, 80 kV, 6.3 mA, 12 s, 0.125 mm voxel size, 0.2 mm slice thickness. Reconstructions of the volume were performed using Planmeca Romexis® Viewer software (Planmeca Group, Helsinki, Finland). After sending the images on the RIS/PACS system, we further processed the images with the software Synapse 3D® (Fujifilm) obtaining Volume Rendering reconstructions.

### 2.3. Histology

The samples of abdominal aorta with the bifurcation of common iliac arteries and inguino-scrotal hernia were immersed for rehydration in Sandison's solution [14] for seven days. Some fragments, calcified and hard to cut, were placed in Kaltek rapid decalcifier for 3 h [15].

The material was then processed according to the procedures of the routine diagnostics. Samples were then included in paraffin to obtain histological sections of 4 µm thickness cut by microtome, subsequently stained with Haematoxylin-eosin, PAS and Giemsa for direct research of resistant alcohol-acid bacilli [16].

### 2.4. Isotopes

By stable isotope analysis, it is possible to determine directly the type of diet of an individual or of a group of individuals, as reviewed in Sehrawat & Kaur, 2017 [17].

Collagen was extracted from the bone samples (phalanx) following the procedures outlined in Longin [18] and modified by Chisholm et al. [19]. Stable isotopes and C:N were measured on a Thermo Finnigan deltaþ XL (continuous flow type), interfaced with a Flash EA1112 elemental analyser via a ConFlo III interface. Both elements were measured together, and a helium-dilution was applied for carbon as the amount of C is far in excess of the amount of N. Carbon- and nitrogen-stable



Fig. 1. The natural mummy of Girolamo Macchi as it appeared after removal of the clothes.

isotopes analysis ( $^{13}\text{C}$  and  $^{15}\text{N}$ ) were performed by Prof. Carmine Lubritto (Second University of Naples).

### 3. Results

#### 3.1. Macroscopy

The external examination of Girolamo Macchi confirmed the well preservation of the natural mummy. It appeared as an old man with scarce adipose tissue of about 1.68 m (Fig. 1). The head, slightly turned on the right, was balding, with the residual blonde hair long on the nape, where we observed an oval bump of about  $3 \times 2$  cm, caused by the accumulation of putrefactive liquids. The nose appeared flattened and the open mouth showed several teeth still present, worn in accordance with the advanced age of the subject (Fig. 2). On the left cheekbone, there was a round depressed lesion of about 2 cm, compatible with one of the medallions found with the mummy, probably laid on the face of the corpse shortly after death when the soft tissues were still malleable. The right arm was reclined on the upper thorax, while the left arm laid on the abdomen, under the navel. The external genital organs were well preserved, and it was possible to observe the penis and a marked enlargement of the left scrotum (Fig. 3) that, once opened, appeared in continuity with the low abdominal viscera; therefore, it was feasible to diagnose a large inguino-scrotal hernia. The legs were totally distended.



Fig. 2. Detail of the bald head, slightly turned on the right, with the residual white hair long on the nape. The nose appeared flattened and the open mouth showed several worn teeth.

Internal organs showed a good state of preservation, revealing severe and diffuse atherosclerosis, present in all the main arteries, with the most impressive aspect at the abdominal aorta up to the bifurcation of the common iliac arteries. The wall of this very well preserved 11 cm segment of aorta was completely calcified, and the lumen appeared partially obstructed by a large plaque of about 2 cm (Fig. 4). This finding is exceptional since it represents one of the most well preserved mummified specimens of artery with a severe and complicated atherosclerotic disease.

Several fragments of calcified atherosclerotic plaques were also found in correspondence of the main vessels in the abdominal cavity close to the spine. Unfortunately, it is not possible to accurately identify which vessels present these pathological calcifications. In fact, due to thanatological phenomena and alterations due to the mummification process, in mummified bodies some structures collapse, others decompose and others dehydrate, modifying their appearance and characteristics. However, as the calcifications have been identified in the lower abdominal region, we can hypothesize that atherosclerosis afflicted the mesenteric and suprarenal districts.

#### 3.2. Imaging

The CT exam evidenced the presence of well-preserved internal organs in the abdominal cavity. In addition, it was possible to identify brain remains in the occipital portion of the skull.



**Fig. 3.** Detail of the well-preserved external genitalia.

It is possible to observe the collapsed penis (blue arrowhead) and a large inguino-scrotal hernia. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Several joints were affected by degenerative joint disease, compatible with the advanced age of the individual; the humeral and femoral head were affected by osteoarthritis. Marginal lipping was visible on several cervical, thoracic and lumbar vertebrae; some vertebral bodies showed Schmorl's nodes. The CT exam evidenced also a calcification of major arteries, in particular the femoral arteries on the anterior side of the proximal femurs and the popliteal arteries on the posterior portion of the knees.

Cone beam CT of the sampled abdominal aorta created a 3D model of the artery and confirmed that the tissue was completely substituted by a hard-calcified material (Fig. 5).

To our knowledge, this represents the first Cone beam study applied to the identification of atherosclerosis and for the reconstruction of the involved vessel in paleopathology.

### 3.3. Histology

The specimen of the abdominal aorta is particularly interesting and with rare comparisons in the paleopathological literature. It was submitted to histological analyses after rehydration in Sandison's solution and rapid decalcification. Then, the specimen was dissected with cuts transverse to the major axis to highlight the whole circumference of the vessel and to study the content of the lumen. At histology, the muscular layers of the wall appeared partially preserved along with the adipose tissue around the vessel; the lumen was partially stenotic by the presence of two large calcified atherosclerotic plaques with a central core composed by cholesterol crystals and necrotic material (Fig. 6). A histological picture of so severe aortic atherosclerosis is uncommon finding in paleopathology and, in addition, the disease appeared diffuse, as we detected vascular plaques and calcifications also in other anatomical regions and, in particular, in a mid-sized artery of the neck. Indeed, a sample obtained by a cut in the laterocervical portion of the neck showed a collapsed mid-sized artery surrounded by abundant adipose tissue and striated muscular layers. The *tunica intima* appeared calcified for the whole circumference (Fig. 7). These findings are overlapping with the alterations revealed at CT, particularly at the abdomen and lower limbs. Instead, the small diameter of the neck vessels identified with histology, along with the quality of the

instrument, did not allow the identification of the microcalcifications by imaging techniques.

Therefore, we have the microscopic confirmation that Girolamo Macchi suffered from a severe and diffuse chronic atherosclerotic disease, compatible with his advanced age and his sedentary lifestyle.

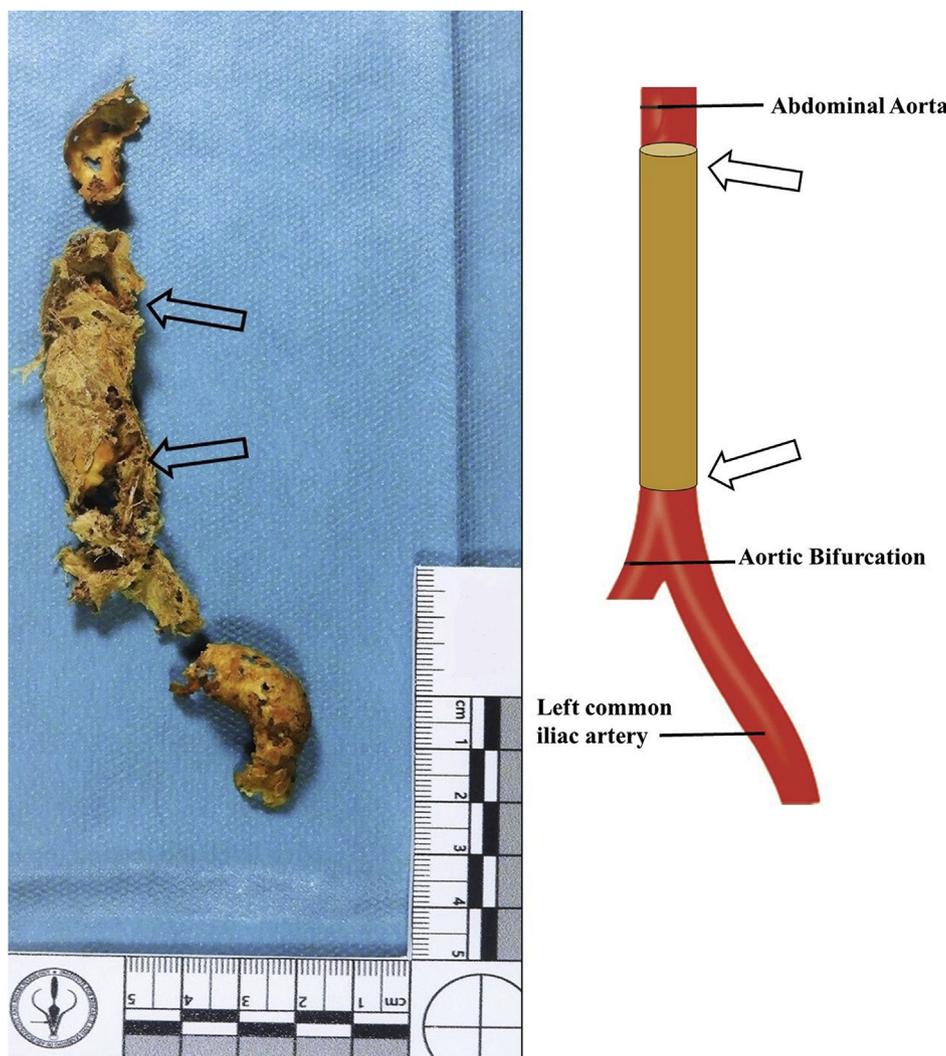
### 3.4. Isotopes

The relationships between the stable isotopes are used to study the animal trophic levels, since there is an increase of about + 2–4‰ for nitrogen and +0.5–1‰ for carbon in the bone collagen between an organism and its “consumer”. Thus, both the  $\delta^{13}\text{C}$  and  $\delta^{15}\text{N}$  values gradually grow during the food chain from plant species with low  $\delta^{13}\text{C}$  and  $\delta^{15}\text{N}$  values, passing through herbivores, carnivores and super-carnivores, with progressively higher values. Therefore, a carnivorous diet based on meat of terrestrial herbivores, such as cattle and sheep, will be characterized by a  $\delta^{13}\text{C}$  around  $-18/20\text{‰}$  and a  $\delta^{15}\text{N}$  of about  $9/11\text{‰}$ , while a plant-based diet will have a  $\delta^{13}\text{C}$  around  $-20/22\text{‰}$  and a  $\delta^{15}\text{N}$  of about  $5/7\text{‰}$  [20]. The Results of stable isotopes analysis of a Girolamo Macchi bone sample show values of  $^{15}\text{N}$  ( $\delta^{15}\text{N} = 11.6$ ) and of  $^{13}\text{C}$  ( $\delta^{13}\text{C} = -18.5$ ) revealing a diet largely based on the consumption of animal proteins. This result is very similar to the data obtained for the Renaissance Italian aristocracy samples, as the Medici Grand Dukes of Tuscany in the 16th-17th century and the nobles of the Aragonese court of Naples in the 15th-16th century (Fig. 8). The Medici had a meat consumption comparable with pure carnivores; the Neapolitan nobles were consumers of meat with an integration of marine fish [20,21].

Paleonutritional data emphasize the high life-style achieved by Girolamo Macchi within Sienese society of 17th-18th century.

## 4. Discussion

The problem of atherosclerosis in Antiquity is a topic that has aroused much debate in recent times. Besides being a fascinating field of research, it has an important impact on modern medicine since atherosclerosis is among the most widespread pathologies in Western populations [1]. Atherosclerosis emanates from a complex interplay of



**Fig. 4.** Specimen of the abdominal aorta up to the bifurcation of the common iliac arteries.

The wall of this very well preserved 11 cm segment of artery is completely calcified, and the lumen appeared partially obstructed by a large plaque of about 2 cm (arrows) (left panel). Illustration of the same vascular segment to better orient the specimen (right panel).

genes and environment [22] and the aetiology is certainly multifactorial, but the most important cause remains certainly the diet [23]. The high consumption of red meat and fats and a poor intake of fruits and vegetables, associated to a sedentary life, significantly increase the risk of developing atherosclerotic disease.

Even if in paleopathology the first studies on this topic have been carried out several decades ago [24], until recent time the diagnosis of the disease was based mainly on radiologic analysis, in particular the detection of calcified vessels through CT scan. Some extensive studies that used this approach surprisingly showed high percentages of individuals affected by atherosclerosis [25], concluding that the disease was not uncommon as expected in past populations. However, in our opinion the only use of the imaging techniques entails overestimation of the disease with a risk of identifying too many false positives. In fact, the development of vascular calcification is related not only to atherosclerosis but also to other conditions such as disorders of calcium-phosphorus metabolism, diabetes, chronic micro inflammation, and chronic renal insufficiency [26].

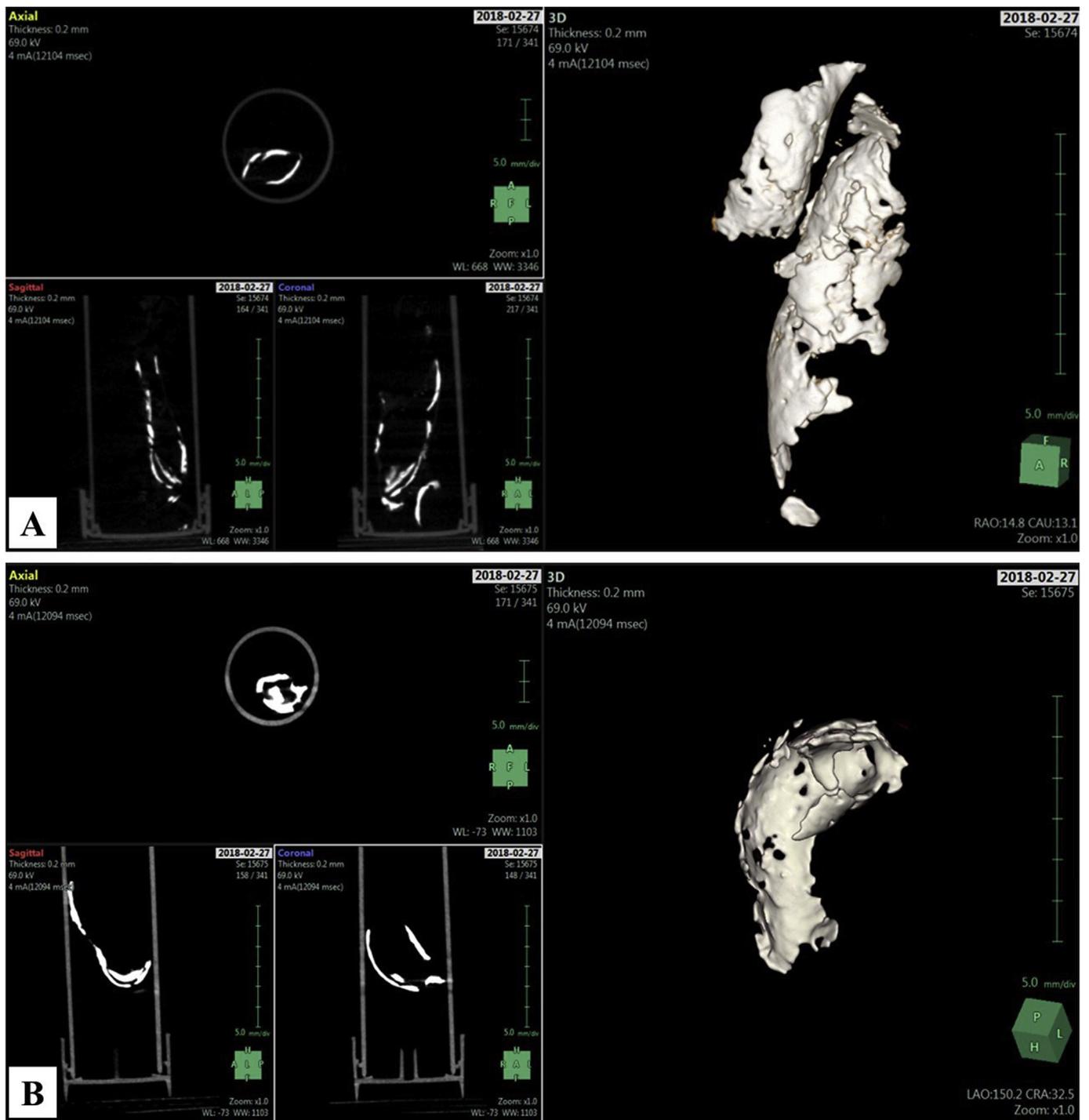
For these reasons, we believe that the most appropriate approach is the combined use of radiological and histological examination.

One of the first papers in which there is a joined macroscopic and microscopic evaluation goes back to 2012 [27]. The finding described in the article, even if referred to a modern forensic case and not to an

ancient body, is comparable to the aorta of Girolamo Macchi. However, we share the methodological approach and the suggestion to put more attention during the archaeological excavations to these vascular structures with arteriosclerosis, which can be disregarded and confused with a root or a small twig.

The mummy of Girolamo Macchi has been studied with a multi-specialised approach characterized by the use of classic imaging techniques, such as CT, and the newer ones like the 3D cone Beam CT, that allow a greater resolution and the virtual reconstruction of the specimen, and the normal methods of pathological anatomy. These techniques confirmed that the ‘Major Writer’ suffered from some diseases typical of the advanced age; he died in fact at 86 years, a surprising age for the time. The skeleton showed degenerative joint disease of the spine and other major joints, some Schmorl’s nodes and the body presented a large inguino-scrotal hernia.

The severe and widespread atherosclerosis, confirmed by histology, represents a striking finding with few comparisons in paleopathology, as for the good preservation of the vessels and the severe degree of the disease. We know that Girolamo Macchi, as confirmed by the paleo-nutritional study with stable isotopes, belonged to the social élite that had a ‘privileged’ diet regimen compared to the mean of his compatriots, ranking among the noble Renaissance courts, as confirmed by his very meat-rich diet. The aetiology of his severe atherosclerotic disease

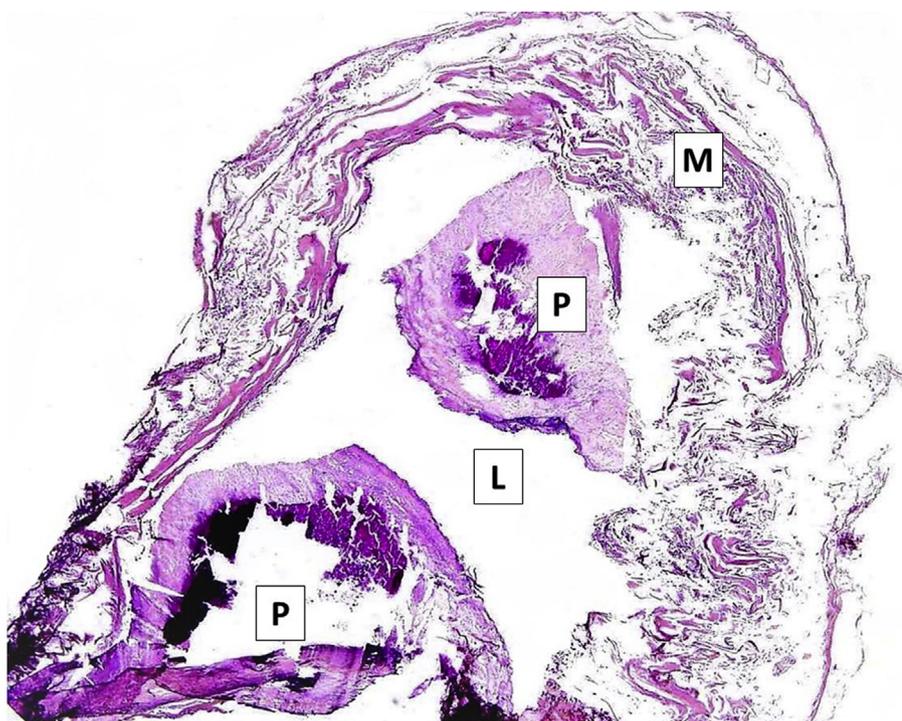


**Fig. 5.** Cone beam CT images. Post-processing of the volume using Synapse 3D. (A) The aortic artery wall appears thickened; calcifications are present, with partial lumen narrowing. (B) The iliac artery presents a calcified plaque, which appears extremely radiopaque and well-circumscribed.

should be related to a diet rich in saturated fat, a sedentary lifestyle and the advanced age. These same risk factors are also shared by Ferrante I of Aragon, King of Naples (1423–1494), whose mummy, studied a few years ago, presented a severe obesity. A sample of the right common carotid artery appeared distorted and calcified, with an irregular and bumpy wall due to severe atherosclerosis; however, the lumen was open. Atherosclerosis was confirmed by the histological findings in terms of an intense red core of oil red-positive amorphous material, surrounded by a foamy substance (the atheroma) lying on a well-preserved elastic wall [28].

Nowadays, we know that the calcification of the arteries of the neck (in particular the carotid arteries) is a very risk factor for ischemic stroke and dementia; stroke in fact is one of the most common cause of death and the leading cause of permanent disability in the U.S. [29].

Despite the severity of the disease, Macchi died at an age seldom reached at that time, and his numerous writings do not reveal any neurological or motor symptoms. Indeed, in his holographic will written in the same year of his death, requiring his burial with the other two mummified individuals, he affirms being ‘*healthy, also sane, by the grace of God, and in full command of my mental faculties*’ [30].



**Fig. 6.** Histological slide of the abdominal aorta. The circumference of the artery is shown. The muscular layers of the wall are partially preserved (M) along with the adipose tissue around the vessel. The lumen (L) appeared partially stenotic by two calcified atherosclerotic plaques (P) composed by cholesterol crystals and necrotic material (H&E, 40X).

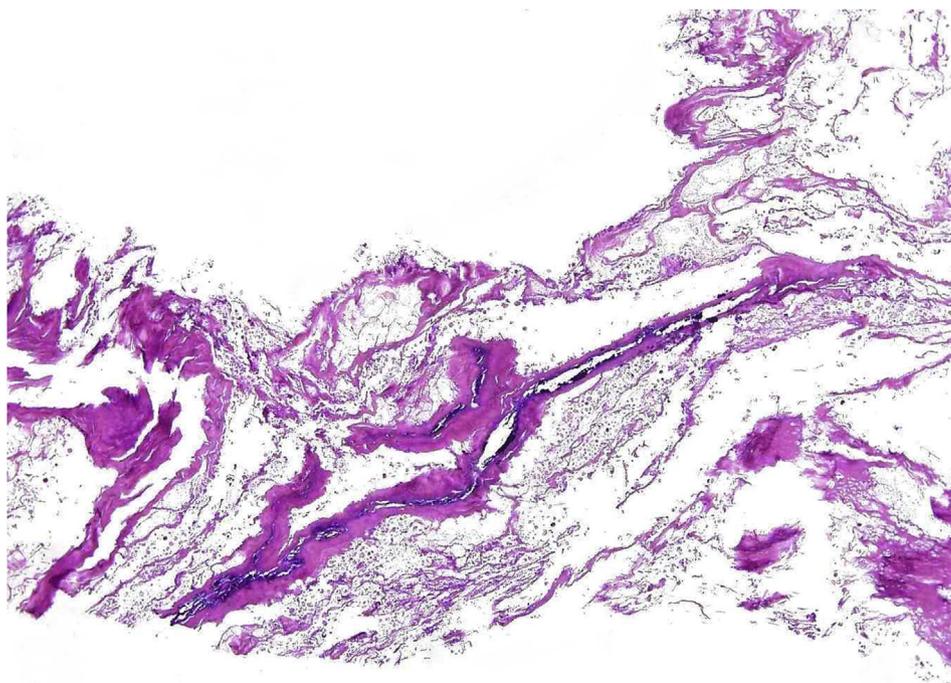
It is possible to affirm that although the degree of atherosclerosis was severe, complicated and at high risk for fatal or disabling pathologies, the disease was probably not symptomatic and did not cause serious problems to the 'Major Writer' of the Hospital of Santa Maria della Scala.

#### 4.1. Conclusions

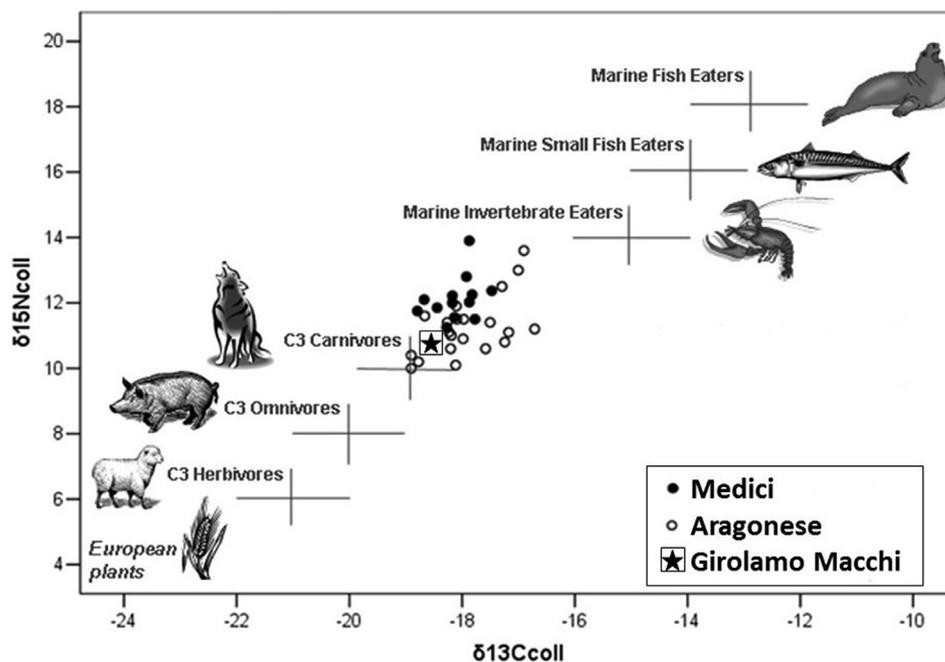
The macroscopic and autoptic study evidence that Girolamo Macchi was affected by severe chronic atherosclerotic disease, with multiple calcifications stenosing the lumen of the vessels, in particular the

lumbar aorta and the iliac arteries. The diagnosis was confirmed by imaging techniques (CT and 3D Cone Beam Scan) and by histology. The multidisciplinary approach, combining macroscopic, radiological and histological analysis, is the most correct method to detect atherosclerosis in mummified remains, as the only imaging techniques do not seem sufficient to define a correct diagnosis.

Based on the historical data and on the paleonutritional studies, this individual was exposed to modifiable risk factors for developing atherosclerosis, as a sedentary lifestyle with an alimentation rich in protein intake, and to nonmodifiable risk factors, consisting in the advanced age and male sex. This case confirms that atherosclerosis is also



**Fig. 7.** Specimen from the laterocervical portion of the neck. The centre of the image is occupied by a collapsed mid-sized artery; the *tunica intima* is composed by a dark basophil material (i.e. the calcification) for the whole circumference. The vessel is surrounded by abundant adipose tissue and striated muscular layers (H&E, 100X).



**Fig. 8.** The position of Macchi ratios of  $^{15}\text{N}$  and  $^{13}\text{C}$  is in relation to the samples from the nobles of the Neapolitan Aragonese court and from the Medici Family of Florence.

The central position of Macchi is evident.

a disease of ancient times. The presence of atherosclerosis in pre-contemporary individuals could suggest that the disease may not only be uniquely characteristic of a specific diet or lifestyle, but it could be also an inherent component of human ageing.

This case is of great importance as the exceptional state of preservation of the abdominal aorta allowed a careful macroscopic and microscopic evaluation, which has only one similar comparison in paleopathological literature [6]. In addition, we have a chance to study the autograph sources of Girolamo Macchi where he affirms to be in good mental and physical health, which represents a real 'medical record' of the patient.

Additional future surveys will help to clarify the history of this disease in the past, especially with the help of paleogenetic, as demonstrated by Shin and colleagues [31], an adjunct modality to diagnose the ancient chronic atherosclerotic disease.

#### Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.atherosclerosis.2018.11.028>.

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