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RENAISSANCE MUMMIES IN ITALY*

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SUMMARY

The paleopathological study of 40 Italian Renaissance mummies has allowed us to perform about 20 diagnoses, of which 5 concern infectious (smallpox, hepatitis, condyloma, syphilis and pneumonia), 4 metabolic (obesity, atherosclerosis, gallstones and uric acid nephrolithiasis), 2 articular (DISH and rheumatoid arthritis) and 2 neoplastic (skin epithelioma and colon adenocarcinoma) diseases.
The mummy of an anonymous child, dated back to the 16th century (C14=1569±60), presented a diffuse vesiculo-pustular exanthema. Macroscopic aspects and regional distribution suggested smallpox, while EM revealed many egg-shaped, virus-like particles (250 × 50 nm), with a central dense core. Following incubation with anti-smallpox virus antiserum and protein A-gold complex immunostaining, the particles resulted completely covered with protein A-gold. These results clearly show that this Neapolitan child died of a severe form of smallpox some four centuries ago. The mummy of Maria of Aragon, Marquise of Vasto (1503-1568), revealed on the left arm an oval, cutaneous ulcer (15x10 nm) with linen dressing. Indirect immunofluorescence with anti-treponema pallidum antibody identified a large number of filaments with the morphological characteristics of fluorescent treponemes. EM evidenced typical spirochetes, with axial fibril. These findings clearly demonstrate a treponemal, probably venereal, infection. The mummy of Ferrante I of Aragon, King of Naples (1431-1494), revealed an adenocarcinoma extensively infiltrating the muscles of the small pelvis. A molecular study of the neoplastic tissue evidenced a typical mutation of the K-ras gene codon 12: the normal sequence GGT (glycine) was altered into GAT (aspartic acid). At present this genetic change is the most frequent mutation of the K-ras gene in sporadic colorectal cancer. The alimentary "environment" of the Neapolitan court of the XV century, with

Key words: Mummies - Paleopathology - Renaissance - Italy

its abundance of natural alimentary alkylating agents, well explains this acquired mutation.
These and other diseases as, for example, a fatal puerperal complication, a thyroid goiter, a case of Wilson's cirrhosis, some cases of anthracosis and other peculiar traumatic conditions, such as a mortal stab-wound, can elucidate the pathocenosis of the wealthy classes of the Italian Renaissance.

Introduction

Contrary to common belief, mummies in Italy, especially single mummies, are quite numerous[1]. According to a recent survey there are 315 preserved bodies of Saints, including at least 25 mummies[2]. The mummies are distributed over the whole Italian territory from north[3] to south[4], where the most important collections are found. The burials, which represent extremely precious paleopathological material, range from the medieval period, through the Renaissance, to more recent times. The samples vary from a small number to several thousands of individuals.

Let us now describe some cases of Renaissance mummies, well studied from a paleopathological point of view.

The mummies of Arezzo (Tuscany)

The restorations of the floor of the Basilica of San Francesco in Arezzo (Tuscany), well known for the frescoes of Piero della Francesca (1412-1492), revealed some wooden coffins containing nine well preserved natural mummies, dated back to the sixteenth century[5]. The mummy of a young lady, aged 20-30 years, in a precious Renaissance dress (Fig. 1), showed an enormous enlargement of the abdomen. Digital radiography revealed sacral spina bifida and a large pubic diastasis (2 cm). Total-body helical computed tomography revealed a well nourished body with swollen breasts, while virtual abdominal endoscopy showed, in the left hemi-abdomen, a large, oblong, hollow mass ($15 \times 10 \times 4$ cm). To avoid autopsy, a minimally invasive laparoscopic examination was performed; using an optic system we entered the abdominal cavity and, by laparoscopic scissors and clamp, we removed samples of the mass. Histology showed smooth muscle fibers and fibrous tissue. These findings are consistent with an immediately postpartum uterus, which also explains the large diastasis of the pubic symphysis. The most likely hypothesis concerning the cause of death is a puerperal complication. The archives, reporting on the burial of a woman who died immediately after delivery, support this scenario[6].

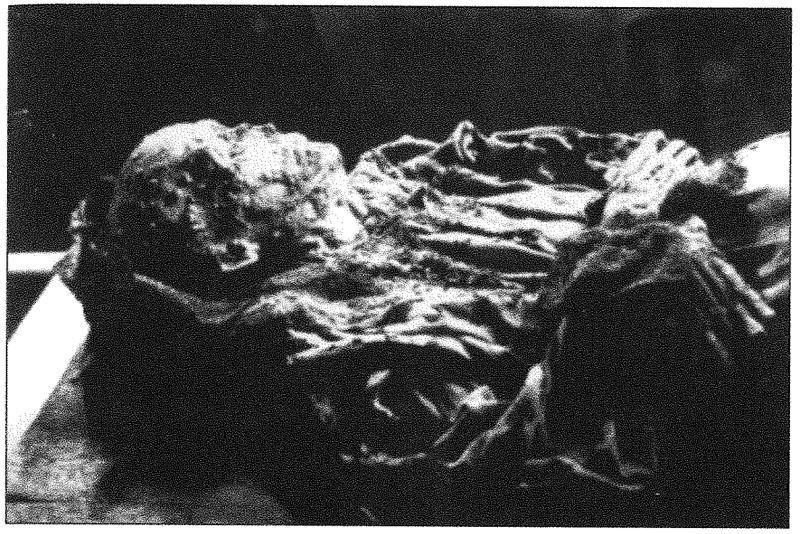

Fig. 1 - Anonymous natural mummy from Arezzo (Tuscany), in her precious Renaissance dress, nicknamed "the lace lady".

There is also a typical case of rheumatoid arthritis in an anonymous woman of about 50 years of age, characterized by bony ankylosis and marginal erosions of the carpo-metacarpal articulations and severe erosive lesions with deformation of the shoulder joints[7].

The mummies of S. Domenico Maggiore (Naples)

The Basilica of San Domenico Maggiore, which dates back to the beginning of the 14th century, is one of the largest and most important churches in Naples. The humanist Giovanni Pontano and the philosophers Tommaso Campanella and Giordano Bruno studied in this Abbey. Saint Thomas Aquinas taught in the annexed convent of the Dominicans.

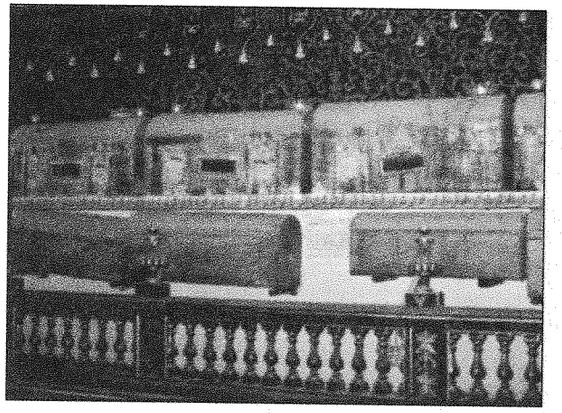

Fig. 2 - Basilica of S.Domenico Maggiore (Naples): suspended gateway with sarcophagi of the Aragonese kings (15th 16th centuries).

The impressive Sacristy of San Domenico Maggiore, in a suspended gateway close to the vault (Fig. 2), contains 38 wooden sarcophagi with the bodies of 10 Aragonese princes and other Neapolitan nobles, who died in the 15th and 16th centuries[8]. In particular they include the Aragonese kings Alfonso I (who died in 1458), Ferrante I (1494), Ferrante II (1496), Queen Giovanna IV (1518) and Isabella of Aragon, Duchess of Milan (1525), who had Leonard da Vinci at her court.

The majority of the individuals had been embalmed (Fig. 3) and this is certainly not surprising, considering the high social class to which the individuals buried in San Domenico be-

Fig. 3 - Artificial mummy of Antonio d'Aragona, Duke of Montalto (1584).

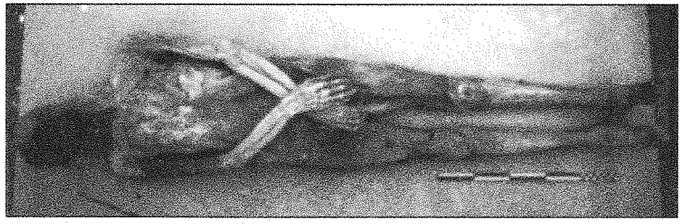

Fig. 4 - Natural mummy of Ferdinando Orsini, Duke of Gravina (1548).

longed. From the physician Ulisse Aldrovandi we learn that during the Renaissance the European kings and great personages used to entrust embalming of their bodies to their doctors and surgeons[9]. The very complex evisceration and embalming methods indicate long-practiced and diffused customs but some well preserved individuals show no apparent signs of embalming (Fig. 4). In this case the natural mummification of the bodies can probably be attributed to the very dry microclimatic conditions of the Basilica[10].

The following are some of the most important paleopathological cases from this series.

The mummy of an anonymous 2 year old boy, whose death dates back to the mid sixteenth century (14C: 1569 - 60), presented a diffuse vesiculo-pustular exanthemous skin eruption (Fig. 5). Macroscopic aspects and regional distribution suggested a case of smallpox. This possibility was confirmed by light microscopy and indirect immunofluorescence with anti-vaccinia virus antibody. Electron microscopy revealed, among the residual bands of collagen fibers, pyknotic nuclei, and membrane remains with rare desmosomes, many egg-shaped, dense virus-like particles (250 × 50 nm), composed of a central core surrounded by a low density area. Following incubation with human anti-vaccinia virus antiserum, after protein A-gold complex immunostaining, the particles were completely covered by protein A-gold (Fig. 6). These results showed that the antigenic structure of the viral particles was well preserved and that this Neapolitan child died of a severe form of smallpox some four centuries ago[11].

Fig. 5 - Detail of face with vesiculo-pustular exanthema typical of smallpox in a 2 years-old child.

The study of a case of treponematosis in the mummy of Maria of Aragon (1503-1568), marquise of Vasto in southern Italy, appeared to be particularly interesting. Famous for her beauty, this noblewoman of the Italian Renaissance belonged to the intellectual and religious circles of Ischia, which also included a friend of Michelangelo's, the poetess Vittoria Colonna. An oval 15 × 10 mm cutaneous ulcer covered by a linen dressing with ivy leaves appeared on the left arm of the mummy. Indirect immunofluorescence with human anti-treponema pallidum antibody identified a large number of filaments with strong yellow-green fluorescence and the morphological characteristics of fluorescent treponemes (Fig. 7). Some morphological aspects typical of the spirochetes, as for example the axial fibril, were evi-

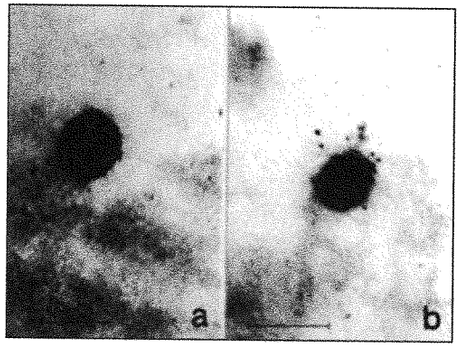

Fig. 6 - Ultratin section of skin incubated with anti-vaccinia virus antiserum followed by protein A-gold. a: dense particle of smallpox virus completely covered by protein A-gold; b: partially labelled particle. (Scale bar: 300 nm).

denced by the ultrastructural study. Immunohistochemical and ultrastructural findings clearly demonstrated treponemal infection and the cutaneous ulcer was typical of a third-stage luetic gumma. Venereal syphilis was the most probable diagnosis[12]. This discovery is extremely important since it dates back to the

Fig. 7 - Intense, positive, indirect immuno-fluorescence reaction with human anti-Treponema pallidum antibody: heaped or isolated treponemes of various sizes (400×).

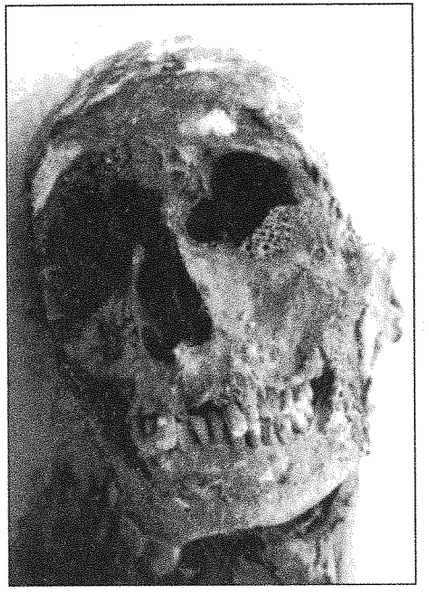

Fig. 8 - Malignant tumor destroying the right nasal bone and the orbit in the mummy of Ferdinando Orsini (1548).

16th century and can help to clarify the biology of treponema in the epidemic phase of the disease.

Molecular biology demonstrated that small DNA fragments could be extracted and could be PCR amplified[13]. We identified a 24 base pair DNA sequence with 100% complementarity with the ORF2 capsid region of the hepatitis E virus genome[14]. This problematic sequence seems to be quite frequent in the mummy's DNA and characterizes three individual amplicons, which we examined, all contained this tract. The hepatitis E virus has no DNA stage, so probably a portion of the viral mRNA was integrated into the host genome by reverse transcription due to the presence of a retrovirus or by retroposition[15]. These two events do not only refer to the life and times of Maria of Aragon, but can be applied to her ancestors as well.

Another important paleopathological case is that of Ferdinando Orsini, Duke of Gravina in Apulia, who died in 1549. The mummy presents wide erosion of the upper orbital margin and the glabella, and complete destruction of the right nasal and retro-orbital bones (Fig. 8). Histology showed solid neoplasia, with cords of spindle-shaped cells destroying compact and spongy bone and forming osseous lacunae, with no bone reaction. A widely destroying skin epithelioma seems to be the most probable diagnosis[16].

The artificial mummy of Ferrante I of Aragon, King of Naples (who died in 1494 at 63 years of age) was submitted to autopsy which revealed in the pelvis a fragment of a hollow muscular organ reaching the dimensions of 6x4x1cm after dehydration. Histologically, neoplastic epithelial cells disposed in cords, nests and glands were disseminated in a fibrous stroma containing scattered striated muscular fibers (Fig. 9). The cells were tall, crowded, with abundant cytoplasm and pseudo-stratified pleomorphic hyperchromatic nuclei. The scant mucus was limited to the pseudoglandular formations, as appeared from the specific Alcian blue staining. The use of a monoclonal antibody versus pancytokeratin displayed strong intracytoplasmic immunoreac-

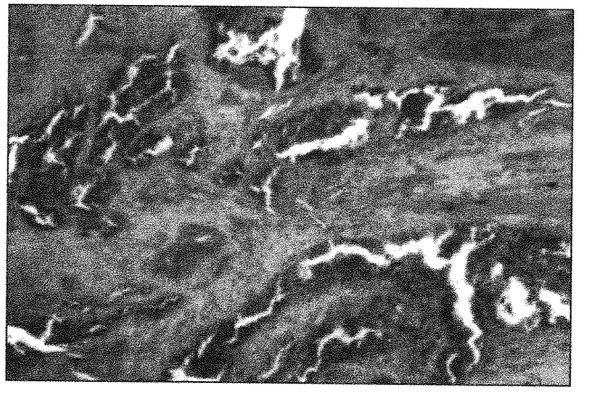

Fig. 9 - Metastatic adenocarcinoma with pseudo-glandular lumina (200×) in the mummy of King Ferrante I d'Aragona (1492).

tivity of the tumoral cells. The ultrastructural study evidenced well preserved pleomorphic nuclei with indented membranes. These results clearly indicate a mucinous adenocarcinoma infiltrating the muscular-fibrous layers of the pelvis.

The site of the primary neoplasm was at first impossible to establish since the histological features only suggested prostatic adenocarcinoma or an adenocarcinoma of the digestive tract[17].

As colorectal tumors are characterized by frequent mutations of the K-ras oncogene and prostatic adenocarcinomas rarely are[18], we decided to investigate the status of the K-ras gene in the DNA extracted from the mummified tumor tissue. The samples were subject to a nested polymerase chain reaction (PCR) protocol designed to yield a 77 base pair (bp) K-ras fragment encompassing codon 12, the main hotspot for mutations in colon cancer. The hybridization with 32P-labelled mutation specific oligonucleotide probes showed the presence in the tumor sample of a K-ras codon 12 point mutation. The normal sequence GGT (glycine) was altered to GAT (aspartic acid). This is the first time an oncogene mutation has been found in an ancient tumor; the data clearly demonstrate that Ferrante I was affected by a cancer of the digestive tract, most probably a colorectal adenocarcinoma[19].

Another well preserved natural mummy, decapitated after death, belonged to a young adult male of about 23 years, identifiable as Ferrante d'Aragona, Duke of Montalto in southern Italy, who died in 1584. Autopsy showed a reduced, but normal shaped, liver with irregular surface due to the presence of single or clumped nodular formations (Fig. 10). Macroscopic observation suggested the diagnosis of cirrhosis, confirmed by basic histology (Hematoxylin-eosin and Masson's trichromic staining) and electron microscopy. In order to identify the possible etiology of this very young cirrhosis, additional techniques routinely used in pathology were performed. HBV infection (immunohistochemistry), hemochromatosis (Perls' method), accumulation of (1-tripsin (Pas/Pas-Diastasis) and Wilson's disease (Rodamina) were investigated. Histochemical rodamina staining, specific for copper, revealed a heavy accumulation of this metal in the liver, suggesting that Wilson's disease was the cause of the cirrhosis[20].

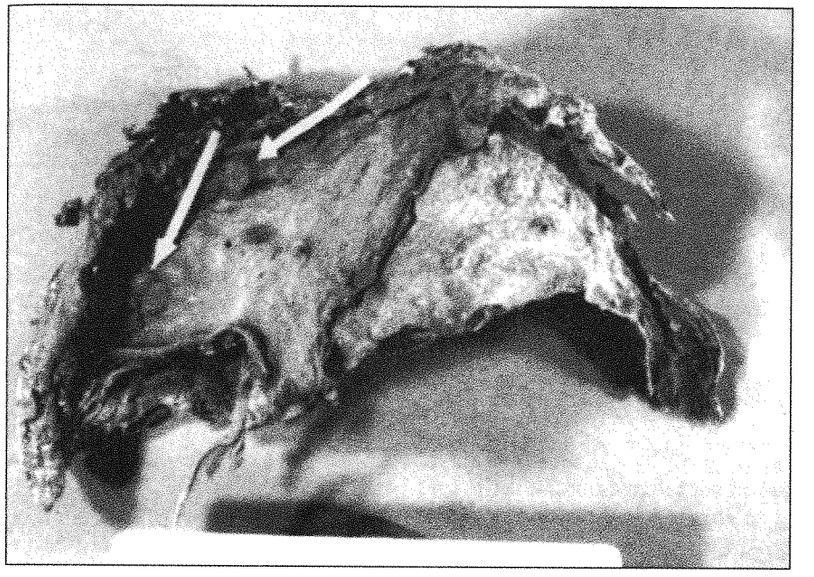

Fig. 10 - Liver cirrhosis (Wilson's disease) in the mummy of Ferrante d'Aragona.

The mummy of Luigi Carafa, prince of Stigliano (1511-1576), had diffuse calcification of the anterior longitudinal spinal ligament on the right side of the midthoracic spine with bony bridges between the vertebrae, calcification of the nucleus pulposus and diffuse exostoses at the elbows, shoulders, hips and knees including also a calcaneus spur; this is a very typical case of the ossifying diathesis known as *diffuse idiopathic skeletal hyperostosis* or DISH[21].

Other pathological conditions we wish to point out in the Renaissance mummies of the Basilica of Saint Domenico Maggiore are:

several cases of obesity, also in young people[22];

severe atherosclerosis of the common carotid arteries, with a large atheromatous plaque (Oil Red +), in the mummy of the king Ferrante I (Fig. 11)[23];

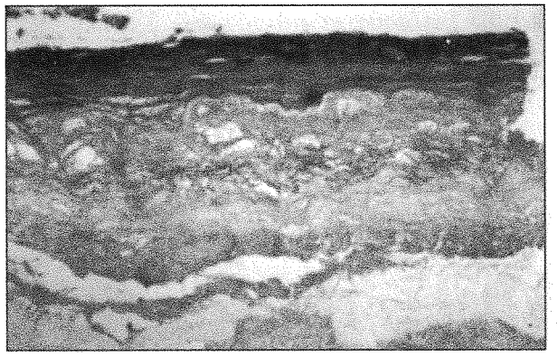

Fig. 11 - Common carotid artery of King Ferrante I d'Aragona (1492) with a large atheromatous plaque.

a case of calculosis of the gall-bladder, with chronic colicystitis[24];

a large condyloma acuminatum of the right inguinal region, in the mummy of Maria d'Aragona[25];

three cases of severe pulmonary anthracosis and some cases of pneumonia[26] (Fig. 12);

a mortal stab-wound, with surrounding hemorragic infarction (Fig. 13), between the eighth and the ninth left rib in the

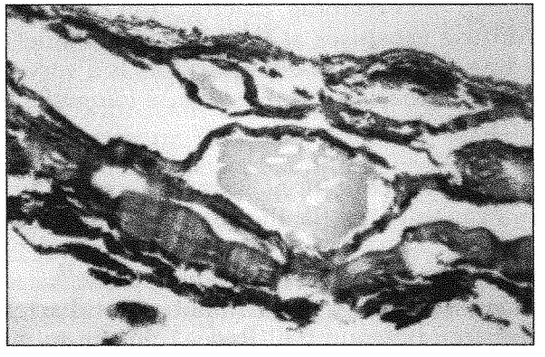

Fig. 12 - Pneumonia and anthracosis in the lungs of Ferdinando Orsini (1548).

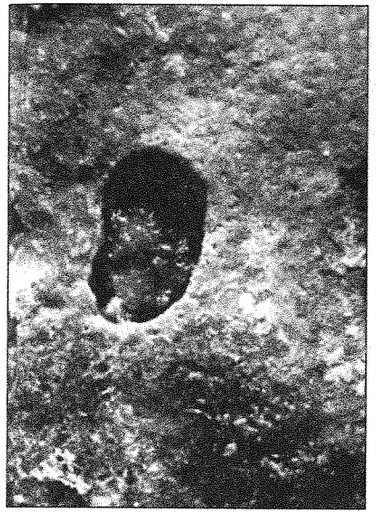

Fig. 13 - Mortal stab-wound, with surrounding hemorragic infarction, in the mummy of an anonymous gentleman of the 16th century.

mummy of an anonymous gentleman who died at the age of about 27 in the second half of the sixteenth century[27].

Other Italian mummies

The natural mummy of a young adult male of about 25 years, housed in the church of Santa Maria della Grazia (Fig. 14) in Comiso (Sicily) and dated at 18th century, revealed a large mass in the thyroid area (Fig. 15). The histological study revealed numerous circular follicles embedded in fibrous tissue, containing amorphous periodic acid Schiff (PAS) positive-staining material. Immunohistochemical stains showed strong reactivity with anti-thyroglobulin antibody. These data confirmed the nature of the tissue as thyroid and the macroscopic diagnosis of thyroid goiter[28].

Finally, a case of nephrolithiasis, with a large round stone of uric acid still in situ (Fig. 16), was found in the mummy Pandolfo III Malatesta (1370-1427), prince of Fano and famous Renaissance leader of mercenary troops[29].

Fig. 14 - An impressive overview of the natural mummies of the church of S. Maria della Grazia in Comiso (Sicily).

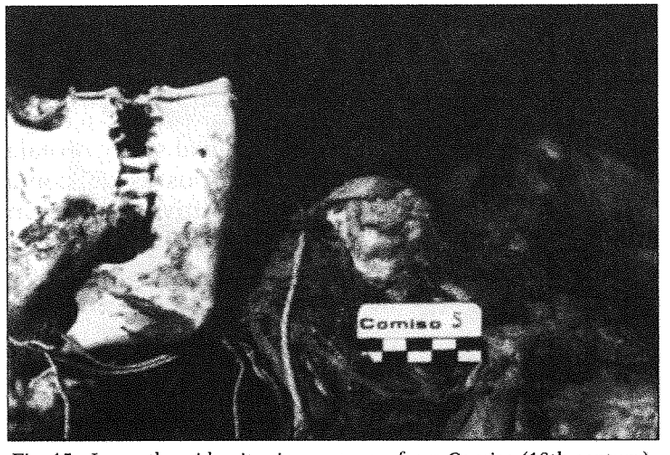

Fig. 15 - Large thyroid goiter in a mummy from Comiso (18th century).

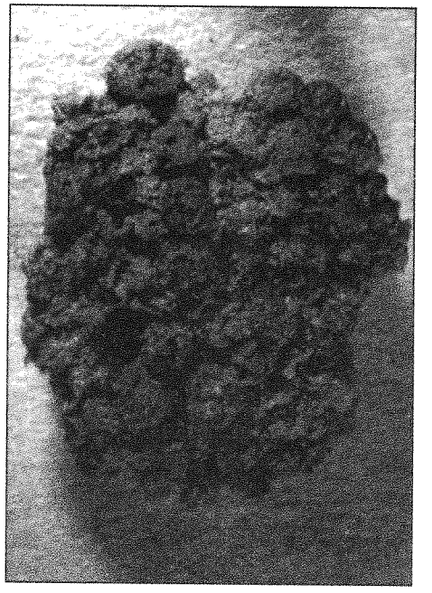

Fig. 16 - Large, moriform stone of uric acid in the mummy of Pandolfo III Malatesta, prince of Fano (1427).

Conclusions

The paleopathological study of 40 Italian Renaissance mummies allowed us to perform about 20 diagnoses (Table 1).

The lady of Arezzo represents a well documented, dramatic example of one of the most frequent causes of death in women during the pre-antibiotic era.

The alimentary regimens of the Italian Renaissance courts, and in particular of the Aragonese court of Naples, with their massive intake of sugars, fats and meat, also attested by paleonutrition[30], well explain the prevalence of some acquired metabolic diseases, such as obesity, atherosclerosis, gallstones and uric acid urolithiasis. Furthermore, diffuse idiopathic skeletal hyperostosis (DISH) is a joint disease which seems to be peculiar to obese and diabetic people over the age of 40-50 years[31].

INFECTIOUS DISEASES
Virus infections
Smallpox
Hepatitis E
Condyloma acuminatum
Bacterial infections
Syphilis
Pneumonia
METABOLIC DISEASES
Obesity
Atherosclerosis
Gallstones
Uric acid nephrolitiasis
HEREDITARY DISEASES
Wilson's cirrhosis
JOINT DISEASES
Diffuse idiopathic skeletal hyperostosis (DISH)
Rheumatoid arthritis
ENVIRONMENTAL DISEASES
Anthracosis
TRAUMATIC CONDITIONS
Mortal stab-wound
TUMORS
Skin carcinoma
Colorectal carcinoma
MISCELLANEOUS DISEASES
Puerperal complication
Thyroid goiter
Hepatic fibrosis

Table 1. Pathological conditions diagnosed in the Renaissance Italian mummies.

The presence of a rare case of Wilson's cirrhosis, caused by an autosomal recessive disorder of copper metabolism, can be easily referred to the well known endogamic habits of the Renaissance wealthy classes[32].

As regards infections, syphilis and condyloma acuminatum are two typical sexually transmitted diseases whose presence, in these classes and during the epidemic phase of syphilis, is not so astonishing. Smallpox was endemic in Italy until the first half of this century, with recurrent outbreaks. Epidemics of hepatitis E were reported in sub-Saharan Africa, but in contemporary Italy the presence of E virus appears sporadic. There are indications of a hepatitis E-like illness occurred in Europe during the 19th century and, presumably, even in more ancient times[33]. Bacterial pneumonias are at present, as certainly were in the past, some of the most common bacterial infections and very frequent terminal cause of death.

Rheumatoid arthritis is particularly important because some Authors consider this a disease of very recent introduction in Europe[34]. The mummy of Arezzo, with its well preserved and complete pathological picture dates the disease at least back to the 16th century.

Anthracosis, also severe in young individuals, can be easily attributed to lifetimes spent next to heating fireplaces and oil lamps, which increased the exposure to smoke. Similar findings reported in many other mummies make it clear that air pollution, at least at a local level, is certainly not a recent phenomenon.

Finally, the mortal stab-wound of the young knight is an example of that intentional, inter-personal violence, well known from contemporary romantic literature, present in the Spanish noble classes of the 16th century.

Regard to the incidence of cancer, the study of the mummies of eleven adult individuals from the Abbey of San Domenico Maggiore, with good or excellent preservation, allowed us to diagnose two cases of cancer. The number of available specimens is very limited, however an incidence of neoplastic pathology of 18.8% is not very far from that of 23% we find nowadays. We can conclude that, at least in some particular environmental and life conditions, as in this series of Spanish nobles, cancer in the past must have been not so rare.

The cutaneous cancer of the duke Ferdinando Orsini arose at the internal orbit angle, a classic site for a *rodent ulcer*, since subject to the strong, chronic sun exposure of southern Italy. The genetic change observed the king's tumor represents the most frequent mutation of the K-ras gene in present-day sporadic colorectal cancer and reflects the effects of alkylating agents[35]. Recent studies have focused on the importance of some alkylating agents, such as the endogenous N-nitroso compounds (NOC). An increased intake of red meat, such as beef, lamb or pork, induces a significant 3-fold rise in the fecal NOC levels, with a range of exposure in the feces similar to that of tobacco-specific NOC in cigarette smoke[36]. The study of the alimentary regimens of the Italian Renaissance courts, and in particular of the Aragonese court of Naples, evidences considerable red meat assumption, also attested by the paleonutritional data[37].

Therefore, the alimentary *environment* of the Neapolitan court of the XV century can well explain, with its abundance of natural endogenous alkylating agents, the K-ras mutation causing the cancer which killed the Aragonese king over five centuries ago.

This brief overview clearly shows the importance of the Italian Renaissance mummies, and the studies carried out in the near future will provide extremely important results not only for paleopathology and history of disease in general, but also for a better knowledge of the very complex pathocenosis of that period.

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