Rheumatoid arthritis, Klippel-Feil syndrome and Pott's disease in Cardinal Carlo de' Medici (1595-1666)

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Abstract

Objective

A paleopathological study was carried out on the she skeletal remains of Cardinal Carlo de' Medici (1595-1666), son of the Grand Duke Ferdinando I (1549-1609) and Cristina from Lorraine (1565-1636), to investigate the articular pathology described in the archival sources.

Methods

The skeletal remains of Carlo, buried in the Basilica of San Lorenzo in Florence, have been exhumed and submitted to macroscopic and radiological examination.

Results

The skeleton of Carlo revealed a concentration of different severe pathologies. Ankylosis of the cervical column, associated with other facial and spine anomalies suggests a diagnosis of congenital disease: the Klippel-Feil syndrome. In addition, the cervical segment presents the results of the tuberculosis (Pott's disease) from which the Cardinal suffered in his infancy. The post-cranial skeleton shows an ankylosing disease, mainly symmetrical and extremely severe, involving the large as well as small articulations, and characterized by massive joint fusion, that totally disabled the Cardinal in his last years of life.

Conclusions

The final diagnosis suggests an advanced, ankylosing stage of rheumatoid arthritis.

Key words

Rheumatoid arthritis, ankylosis, tuberculosis, Medici, Florence, Renaissance.

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Received on February 9, 2009; accepted in revised form on March 20, 2009.

Competing interests: none declared.

Introduction

The well-preserved skeleton of Cardinal Carlo de' Medici (1595-1666), the younger son of Grand Duke Ferdinando I (1549-1609) and Cristina of Lorraine (1565-1636), has been exhumed and subjected to careful examination. The cardinal was buried beneath the floor of the Basilica of San Lorenzo in Florence, together with the other members of the junior branch of the family of the grand dukes of Tuscany, which began with Giovanni delle Bande Nere (1498-1526), a famous captain of mercenary troops, and ended with Gian Gastone (1671-1737), the last Medici grand duke.

The Medici were one of the most powerful and influential families of the Italian Renaissance. On the foundations of a successful commercial and banking business, they accumulated long-lasting social power and political prominence, initially in Florence and later in the entire region of Tuscany.

With the generous permission of Dr. Antonio Paolucci, Superintendent of the Museums of Florence, in 2004 the "Medici Project" was officially launched. This is a multidisciplinary research project devoted to the study of the 49 members of the Medici family buried in the Basilica of San Lorenzo, involving research groups from the University of Pisa, the University of Florence and the Superintendency for the Museums of Florence. So far the skeletal remains in twenty tombs, including those of nine children, have been studied (1, 2).

Carlo (Fig. 1) was the third son of Ferdinando I and Cristina of Lorraine and was early in his life directed toward an ecclesiastic career, which lasted more than fifty years, during which he was appointed to various prestigious positions. In 1615, at the age of 20, he became a cardinal under Pope Paolo V and in 1652 he was nominated Dean of the Sacred College of Cardinals. Carlo loved the pleasures of life, however; his favourite pastimes were hunting, feasting, gambling, and gallant conversation. He was passionately fond of music and the theatre, he commissioned and collected works of art, and he had several of the Medici residences restored and redecorated.

Archival documents attest to the fact that Carlo suffered from many diseases during his life. At the age of 8 he was infected with tuberculosis, resulting in the deformation of his cervical column (Pott's disease). In addition, documents inform us that he suffered from an acute joint disorder involving the feet, hands and knees, which began at the age of 24 and was identified by the court physicians as 'gout'; Carlo suffered 18 severe attacks between the age of 35 and 59, and his condition markedly worsened between the age of 60 and 65. Indeed, it appears that the cardinal was totally disabled during the last years of his life; from 1658, when he was 63, he was no longer able to sign letters or documents. In a letter to a nephew dated 4th December 1658 he writes: "*Y(our) H(ighness) please excuse me for not being able to sign in my own hand (writing), because my hand does not function*" (3). From the age of 50 to 70 the cardinal was affected by recurrent bronchitis and he finally died of bronchopneumonia at 71 years of age (3).

The present study discusses the joint lesions observed in the skeleton of this important member of the Medici family.

Materials and methods

The remains of Carlo de' Medici were buried, together with those of his parents Ferdinando I and Cristina of Lorraine and his brother Francesco, in a side chapel of the Basilica of San Lorenzo. His skeleton, as well as those of other family members in San Lorenzo, had already been studied during the Second World War (4), so the remains of Carlo were not located in their original burial place.

The remains are well preserved, with the exception of some missing middle and terminal phalanges of the hands and feet. The bones were first examined macroscopically and then by x-ray at the Careggi Hospital in Florence. The pathological segments were also scanned by CT.

Results

Anthropological study showed the skeleton of a elderly male (more than 60 years of age) with several anomalies and pathologies.

Fig. 1. A portrait of Cardinal Carlo de' Medici by Justus Sustermans (Galleria Palatina).

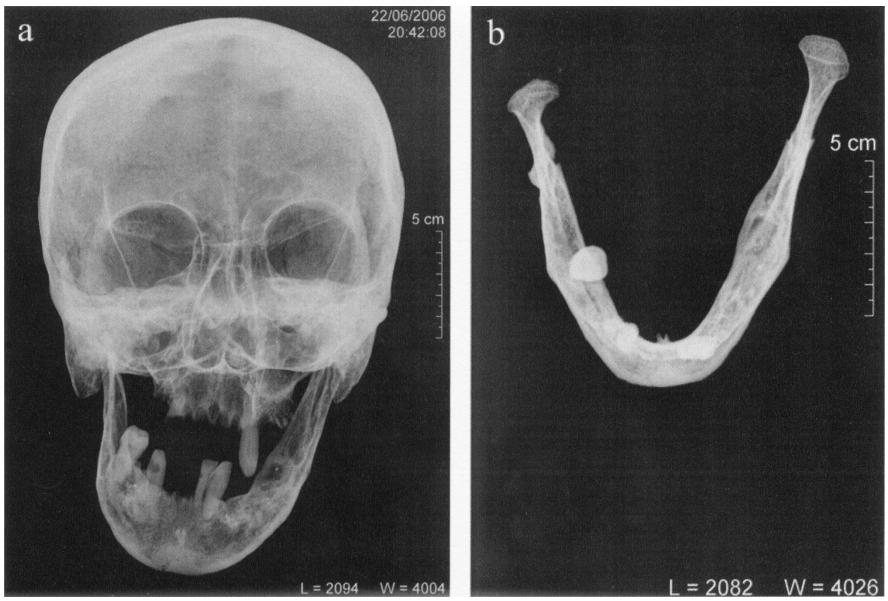

Fig. 2. Antero-posterior projection of the skull showing evident asymmetry of the facial skeleton at the level of the nasal and maxillary bones, which appear larger on the left side: (**a**); marked hypoplasia of the right hemi-mandible corpus of the mandible, visible on x-ray (**b**).

The facial skeleton presents asymmetry of the nasal and maxillary bones, which appear larger on the left side (Fig. 2a). There is marked hypoplasia of the right hemi-mandible corpus and the right ramus (Fig. 2b).

The atlas is totally fused with the occipital bone. The cervical column is fused in a single block from the first to the fifth vertebrae, involving the articular facets, pillars and posterior portions of the vertebral bodies, with narrow disc spaces. The axis is fixed in an abnormal oblique right-directed position (Figs. 3 and 4). This anomaly probably resulted in a chronic torticollis *in vita*.

A second block at the level of C6-C7 and involving the entire vertebral bodies also shows a wedge-shaped collapse, with the formation of an angular kyphosis (Fig. 3b, black arrow). CT demonstrated some osteolytic lesions with no sclerotic margins (Fig. 4b, white arrow).

Several other column fusions involving the articular facets, pillars and posterior vertebral bodies are present: T2 is merged with T3, T7 with T8, T9 with T10, and T11 with T12. Ossification of the anterior right vertebral ligament at the level of the T9 and T10 vertebral bodies led to the formation of a bony bridge. The remaining *vertebrae* are normal.

With regard to the lumbar spine, L5 is fused with a supernumerary L6. Finally, the right innominate bone of the pelvis is fused with the sacrum, while the left sacro-iliac joint is normal (Fig. 5, black arrow).

In the thoracic area, the *manubrium* of the sternum presents marked ossification of the sterno-costal cartilage on both sides, which is more severe on the left. The internal surfaces of most of the ribs show a slight diffuse periostitis.

The right humerus and ulna are totally fused, with the elbow fixed in a flexion of 110°. In addition, the head of the radius is partially fused with the radial notch of the ulna. The right wrist shows total ankylosis of the distal epiphysis of the radius with the carpal bones, which are also fused together, with the exception of the hamate and the pisiform. In the right hand, the second metacarpal is merged with the trapezoid bone and the third metacarpal with the

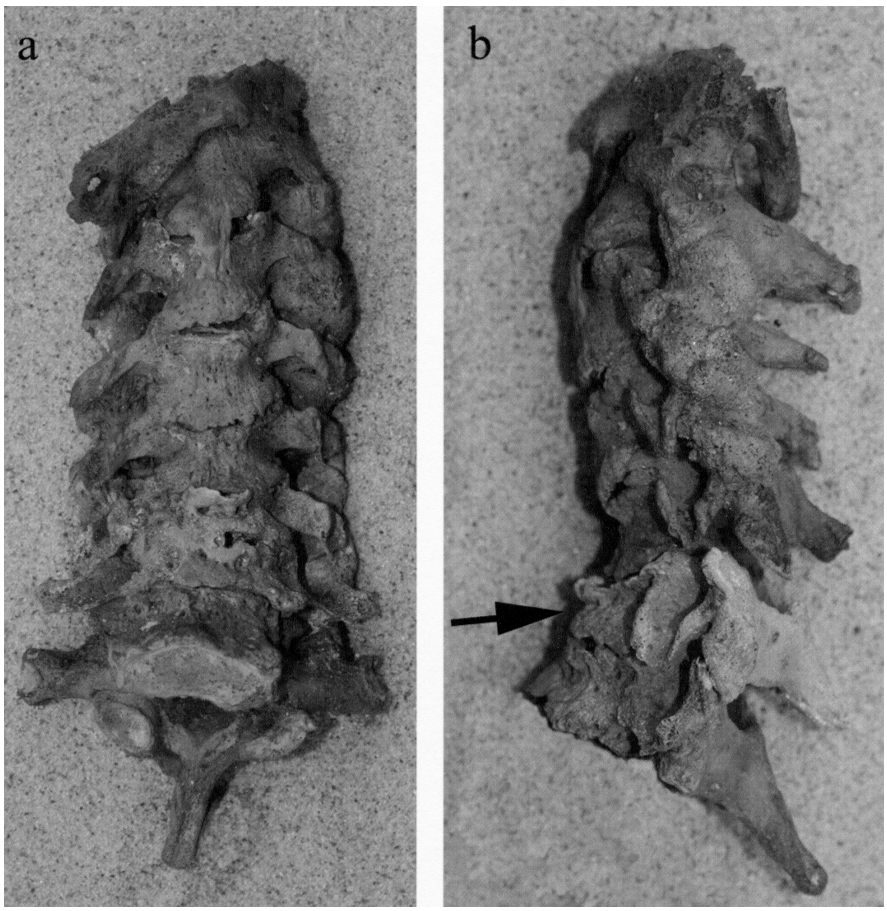

Fig. 3. Ankylosis of the cervical column in a frontal (**a**) and lateral (**b**) view. A block from C1 to C5 and a fusion merging C6 and C7 (**black arrow**) are visible.

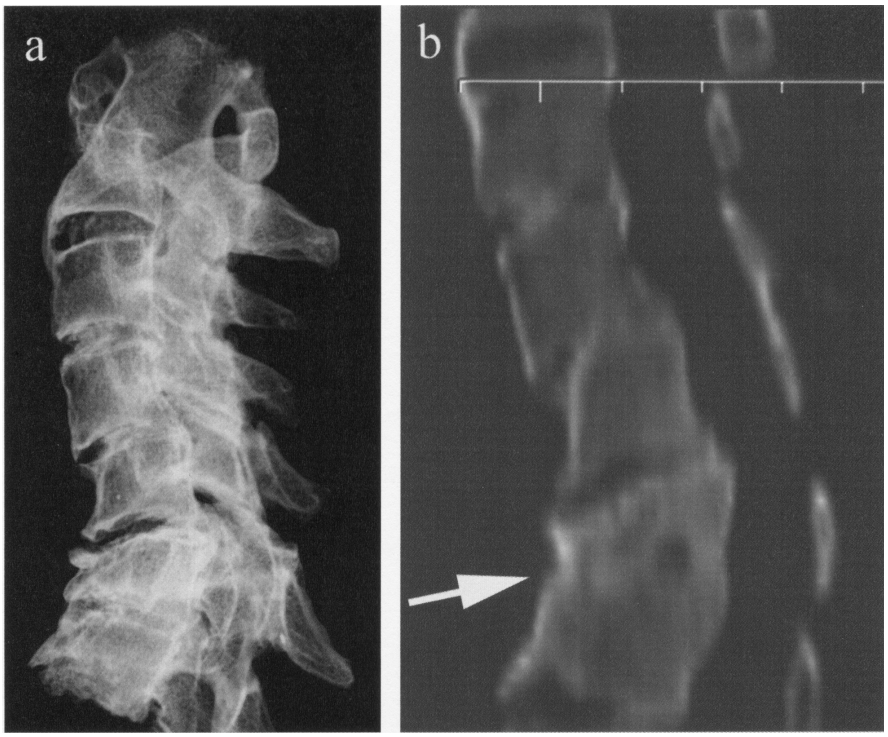

Fig. 4. X-ray latero-lateral projection of the cervical column (**a**) and computed tomography showing osteolytic lesions in C6 (**b**).

capitate bone (Fig. 6a). Ankylosis is also present between the third proximal and middle phalanxes, which are fixed in an antero-posterior curvature (Fig. 6b and c).

In the left arm the elbow joint is normal, but there is fusion of the distal epiphysis of the radius with the ulna, fixing the radial head in the ulna notch, with a small amount of wrist dislocation. The distal radius is merged with the carpal bones (Fig. 6a); moreover, all the carpal bones, with the exception of the pisiform, are fused together (Fig. 6d). In the left hand, ankylosis is present between the fourth proximal and middle phalanxes, which are fixed in an antero-posterior curvature.

In the lower extremities, the knees present fractures that clearly were incurred after death, at the level of the right proximal epiphysis of the tibia and the left distal epiphysis of the femur.

Both femurs are totally fused with the tibiae, so that the knee joints are fixed in a posterior flexion of 90° (Fig. 7a); the patellae are also ankylosed in their respective joints (Fig. 7b and c).

Both feet show total ankylosis between the talus, the calcaneus, and the tarsal and metatarsal bones (Fig. 8a and b).

Several attachments for the muscles and ligaments show marked enthesopathies.

All the skeletal segments, and in particular the lower limbs, are affected by severe osteoporosis.

Discussion

Spine pathologies

Fusion of the cervical spine can be attributed to either a congenital or an acquired (most frequently inflammatory) condition. In the case of Cardinal Carlo, the atlanto-occipital fusion and the absence of bone remodelling and sclerosis in the superior portion of the cervical segment between C1 and C5, as clearly shown by x-ray, support the hypothesis of a congenital disease.

The congenital fusion of two or more cervical vertebrae was first described in 1912 by Maurice Klippel and Andre Feil, in a clinical case characterized by massive fusion of the cervical elements (5). Klippel-Feil syndrome (KFS) has been classified into three types based on the location and degree of fusion

Fig. 5. Ankylosis of the right sacroiliac joint (**black arrow**).

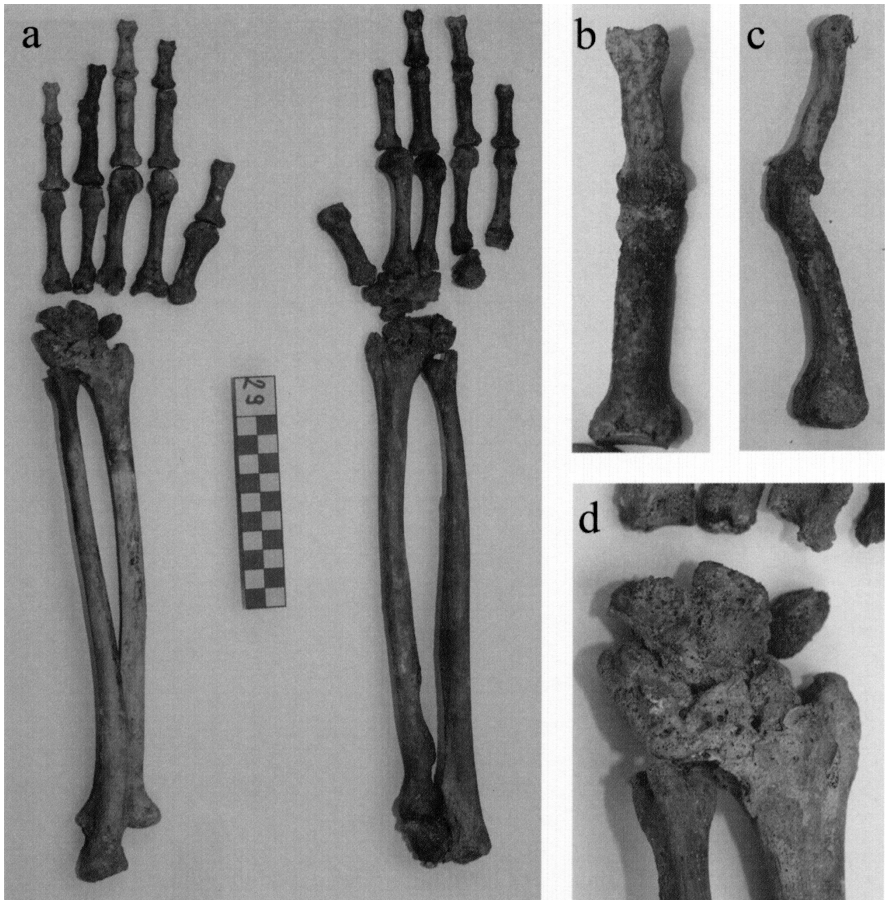

Fig. 6. Ankylosis of the right elbow joint and bilateral fusion of the carpal bones (**a**); ankylosis between the third proximal and the middle phalanx of the right hand, in antero-posterior curvature (**b**, **c**); detail of the left wrist, showing fusion of the distal radius with the ulna and fusion of the distal radius with the carpal bones (**d**); all the carpal bones, with the exception of the pisiform, are fused together.

(6): type I, with involvement of several cervical and thoracic vertebrae, which are fused in a single block; type II, with the fusion of one or two vertebrae; and type III, in which thoracic and lumbar segment anomalies are associated with type I or II KFS. Klippel-Feil syndrome is not a common condition and its aetiology is uncertain; the fusion results from a failure in the segmentation of the spine that can occur between the third and the eighth week of gestation (7).

Klippel-Feil syndrome is frequently accompanied by other anomalies of the skeletal apparatus (8), such as atlantoccipital fusion, malformation of the atlas and axis, platybasia and basilar impression, facial asymmetry, fronto-nasal dysplasia, temporo-mandibular dysfunction, cleft palate, hemivertebrae, *spina bifida occulta*, scoliosis, kyphosis, Sprengel's deformity (a congenital elevation of the scapula due to its failure to descend to its normal thoracic position during fetal development), an alteration in the number of *vertebrae*, or hypodontia (8, 9).

In the paleopathological literature KFS has rarely been reported (for a bibliography, see ref. 10).

The skeleton of Cardinal Carlo de' Medici presents several features that make Klippel-Feil syndrome the most likely diagnosis; based on Feil's classification, this is a case of type III KFS, in which fusion of the cervical spine is associated with the fusion of other elements in the thoracic and lumbar spine. A typical block fusion between C1 and C5 is present; the arches and posterior bodies are included, with narrowing of the inter-vertebral spaces. Other minor fusions are present in the thoracic (T2-T3; T 7-T8; T9-T10; T11-T12) and lumbar (L5-L6) spine. Atlanto-occipital fusion and a variation in the number of lumbar *vertebrae* (6) – both often present in KFS – were also observed. Furthermore, the presence of other skeletal anomalies – marked facial asymmetry and temporo-mandibular dysplasia – supports this diagnosis.

On the other hand, the fusion of two lower cervical elements (C6-C7) in the cardinal's skeleton, with collapse of the vertebral body and angular kyphosis, cannot be linked to KFS, as demonstrated by the massive bone remodelling with sclerosis shown on x-ray and by the wedge-shaped deformation of the C6 body, which is typical of tuberculosis (Pott's disease) (11).

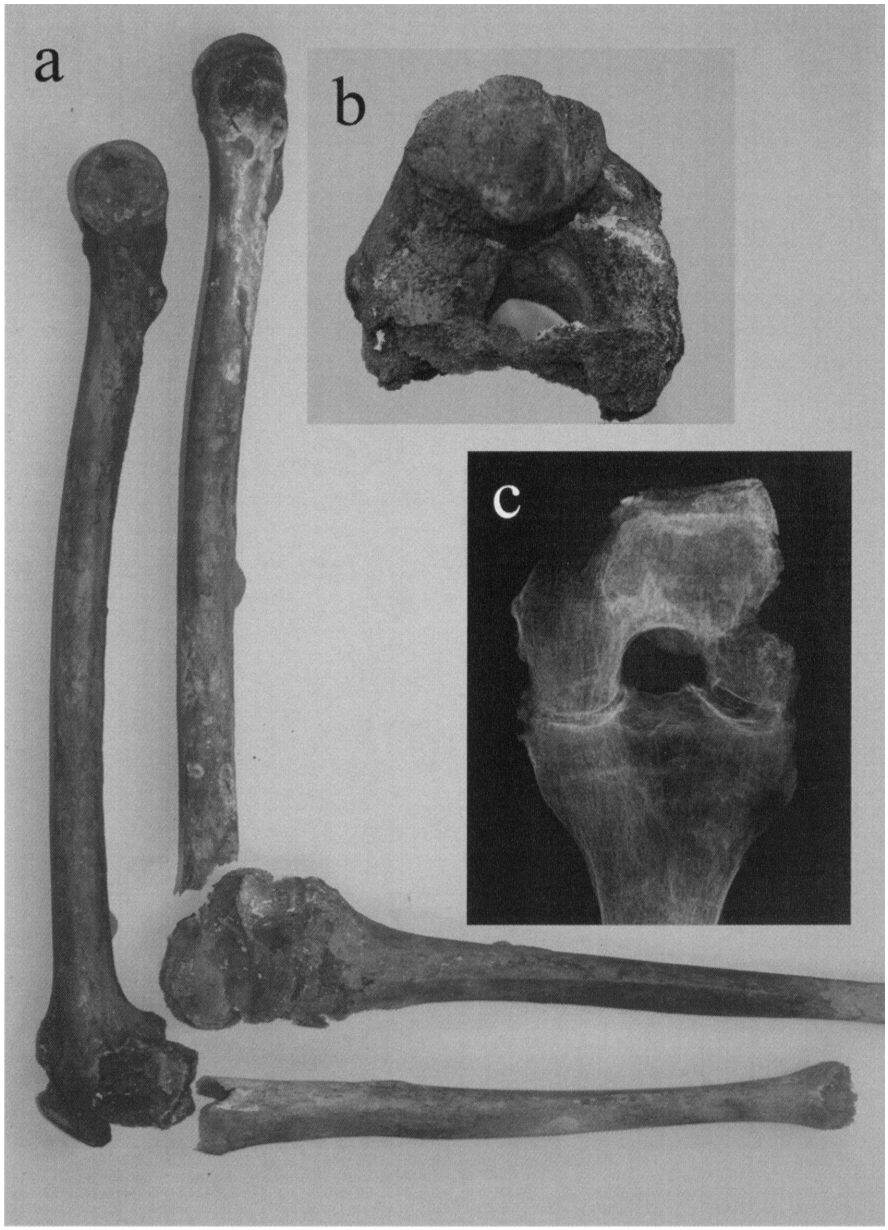

Fig. 7. Bilateral ankylosis of the knee joints, fixed in posterior 90° flexion (**a**); right knee with the patella ankylosed in the articulation (**b**); antero-posterior projection of the left knee joint (**c**).

This fusion can be traced back to Carlo's cervical spine tuberculosis, which included neck *fistula* and initial *gibbus* as is clearly described in the documents of the period (3). The slight periostitis on the ventral surface of the ribs, which has been identified as a possible sign of pulmonary tuberculosis (12), confirms the diagnosis.

Polyarthritis

The post-cranial skeleton shows generally symmetric, extremely severe ankylosing disease involving the large as well as small joints and characterized by: fusion of the right elbow (in flexion at 55°); bilateral fusion of the wrists, carpal bones, and some fingers; fusion of the right sacroiliac joint; bilateral fusion of knees and rotulae (in flexion at 90°); and bilateral fusion of the tarsal and metatarsal bones.

This data, together with the very severe osteoporosis, in particular of the lower limbs (due to non-use), demonstrates the total disability suffered by the cardinal in the last years of his life, as reported in documents from the period. His skeletal lesions reveal severe, symmetrical, ankylosing polyarthropathy. Several diseases were considered in our analysis of the aetiology and the differential diagnosis of Carlo's condition: osteoarthritis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Reiter's syndrome, enteropathic arthritis and chronic gout.

Osteoarthritis could be easily ruled out, because joint fusion is very unusual in OA. The partial fusion of the thoracic and lumbar column affecting only the posterior arches and not the bodies, with no bone remodeling or sclerosis, instead closely resembles the cervical anomalies of KFS.

Rheumatoid arthritis (RA) is a chronic, inflammatory autoimmune disorder affecting the joints symmetrically, in particular the upper and lower extremities. The inflammatory process is characterized by erosion, and can progress to destruction of the juxtarticular ends of the bones and ankylosis. RA affects women more often than men, the incidence today being approximately 1–2% in males and 2–4% in females. Onset can occur at any age, although it is more common in the fourth and fifth decades of life (13).

The first and most commonly involved joints are the fingers, wrists, feet and toes, followed by the more proximal joints of the extremities, such as the knees, elbows, ankles, shoulder joints, hips, cervical spine, and the temporomandibular, sternoclavicular and manubriosternal joints. Symmetrical involvement of the wrists is almost always present in RA, where synovitis leads to fibrous and then bony ankylosis of the carpal bones. For this reason, the carpus is one of the sites where early onset ankylosis is most frequent. Involvement of the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints with swan-neck deformity, is typical in RA as well. Distal interphalangeal (DIP) involvement is more rare. The elbow joint is frequently involved, with loss of extension as an early sign of the disease, and ankylosis in flexion in the more advanced stages. Damage to the shoulder joint is variable and is usually seen in the most advanced cases. Involvement of the knee is common in RA. The affected person tends, when seeking a more comfortable position, to

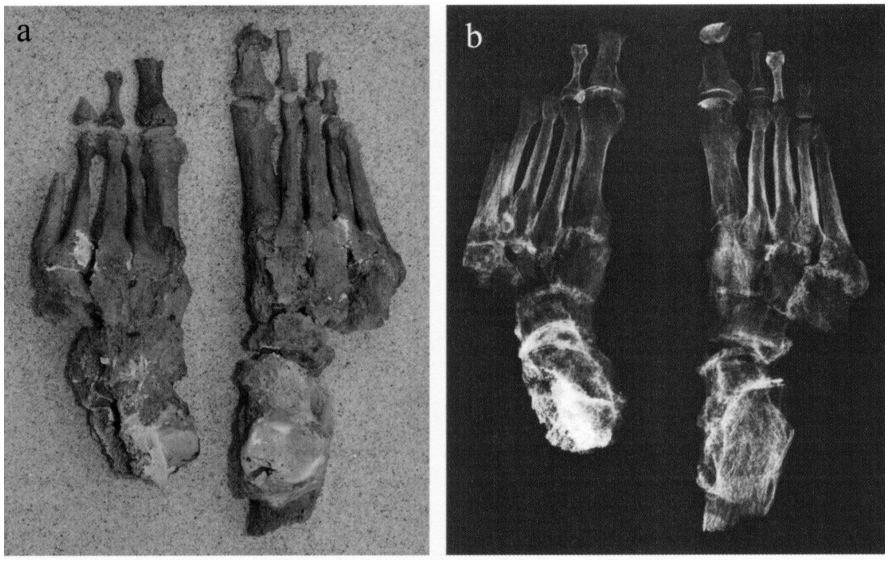

Fig. 8. Bilateral ankylosis of the feet, involving the talus, calcaneus, tarsal bones and all the proximal epiphyses of the metatarsal bones (**a**); antero-posterior projection of the feet (**b**).

flex the joint and with time this results in a loss of extension and fixed flexion of the knee in a bony block. The subtalar and talonavicular joints and the metatarsal heads commonly show diffuse erosion; the hind-foot joints may spontaneously fuse. Involvement of the sacroiliac joint can be seen in advanced cases (14, 15). RA in the spine is rare, and occurs only in the cervical segment, where it produces erosive phenomena and atlanto-axial subluxation (16). Rheumatoid arthritis is usually accompanied by osteopenia and diffuse osteoporosis on x-ray (15).

In the skeleton of Cardinal Carlo the symmetrical and polyarticular features of the disease, the specific joints involved, and the swan-neck deformity in both hands are all hallmarks of RA.

Some authors (17, 18) have posited that articular ankylosis in advanced RA is a consequence of steroid therapy. This hypothesis, based on some ancient cases of erosive RA in North American Indians with a very short life span, does not take into account the presence of older 'patients'. On the contrary, members of the Italian aristocracy who eventually develop RA, like Cardinal Carlo, but who enjoyed the benefits of continuous care can be shown to have reached an advanced stage of ankylosis without the administration of steroids.

In the paleopathologic literature, cases of RA have been reported in ancient Egyptian mummies, medieval Sudanese skeletons, European skeletons from the late Iron Age to the Renaissance, American populations from 3000 BC to 1100 AD, and in Asian remains (for a bibliography, see ref. 19).

The association of rheumatoid arthritis and Klippel-Feil syndrome, although rare, has been reported *in vivo* (20). The skeleton of Carlo de' Medici represents the first documented case in the palaeopathological literature of the coexistence of these two rare conditions.

Psoriatic arthritis (PA) is a rare chronic polyarticular disease that affects around 5-7% of patients with chronic skin psoriasis. It mainly involves the upper and lower extremities, in particular the small joints of the hands and feet, the wrists, ankles, knees and elbows, in a symmetrical pattern with a tendency to ankylosis. Involvement of the distal interphalangeal joints is typical. In the phalangeal and metacarpal bones, the osteolytic phenomena results in telescoping digits; the distal phalanges can assume the characteristic pencil-in-cup deformity. Sacroiliitis (frequently asymmetric) may be associated with spondylitis, sometimes similar to ankylosing spondilitis (21).

Distinguishing between RA and PA is a very difficult task in paleopathology. In this case the absence of spinal involvement or telescopic digits in the hands and feet – both typical features of PA – and

Table I. Lesions detected in the skeleton of Carlo de' Medici and the lesions typical of different arthropathies.

	Carlo de' Medici	Rheumatoid arthritis	Psoriatic arthritis	Reiter's syndrome	Ankylosing spondylitis	Enteropathic arthritis	Chronic gout
No. of joints involved	poly	poly	poly	mono/paucia	spine involvement	paucia	poly
Involvement of hands and feet	yes	yes	yes	yes	no	yes	yes
Symmetrical involvement	yes	yes	yes	no	yes	no	no
MCP and PIP joints affected	yes	yes	yes	yes	no	yes	yes
DIP joints affected	no	no	yes	yes	no	yes	yes
Swan-neck deformity	yes	yes	no	no	no	no	no
Spinal fusion	no*	no	yes	yes	yes	yes	no
Skip lesions	no*	no	yes	yes	no	either	no
Sacroiliitis	yes	frequent	yes	no	yes	yes	yes
Symmetrical sacroiliitis	no	no	no	no	yes	either	no
Enthesopathies	yes	yes	yes	yes	yes	yes	yes
Skin lesions	no	no	severe	moderate	no	mild	yes

Mono: monoarticular; paucia: pauciarticular; poly: polyarticular; MCP: metacarpo-phalangeal; PIP: proximal interphalangeal; DIP: distal interphalangeal.
*Only posterior fusions of Klippel-Feil syndrome.

the presence of diffuse ankylosis, which is uncommon (except in the carpus) in PA, allow us to rule out the diagnosis of PA. Finally, the distal epiphyses of the middle phalanxes of the hands and feet do not show any joint lesions.

Alongside these bone features, a further important observation must be kept in mind. If Carlo de' Medici suffered from psoriatic arthritis, he would also probably have experienced some cutaneous manifestations. A rare form of psoriatic arthritis *sine* psoriasis, in which the onset of rheumatic manifestations precedes by several years the development of skin lesions, has been described (22), but Carlo was suffering from advanced stage arthritis that should necessarily have been accompanied by skin psoriasis. It is unlikely that the highly visible dermatologic manifestations of psoriasis would not have been described, if present, in the reports of the Medici court physicians and ambassadors, which were generally quite detailed. On the contrary, in the many chronicles of the cardinal's life conserved in the Florentine archives, no mention of any dermatologic problems can be found (3).

Ankylosing spondylitis (AS) is a chronic systemic inflammatory disease that primarily involves the axial skeleton. The most obvious manifestation of AS is axial arthritis, such as sacroiliitis or spondylitis. Involvement of the peripheral limb joints is uncommon (23).

In the case of Cardinal Carlo, the absence of axial arthritis and a complete ossification of the spine, which are the main features of AS, and the presence of severe involvement of the hands and feet, which are on the contrary uncommon in this arthropathy, rule out the diagnosis of AS.

Reiter's syndrome (RS) is a rare joint disorder that develops in response to an infection in another part of the body, in particular in the bowels or the urogenital tract. The syndrome is characterized by asymmetrical monoarthritis or oligoarthritis involving the lower as well as the upper extremities. Sacroiliitis and spondylitis are common findings (24). The symmetrical and polyarticular involvement seen in the cardinal's skeleton, however, allows us to exclude a diagnosis of RS.

Enteropathic arthritis is associated with some chronic diseases of the intestinal tract (Crohn's disease, Whipple's disease, ulcerative colitis) and manifests primarily as spondylitis and sacroiliitis. Both the large and the small joints may be affected, in particular those of the lower limbs, but the involvement is pauciarticular and asymmetrical (25). The principal features of enteropathic arthritis – *i.e.* spondylitis and asymmetrical and pauciarticular involvement – were not observed in the skeleton of Carlo de' Medici.

Chronic gout is a crystal-induced arthropathy associated with tophus formation and bone and joint destruction, and is most commonly seen in middle-aged males (26). The chronic poly-articular form of tophaceous gout can mimic polyarticular diseases, including RA (27). However, in chronic gout the joint involvement is asymmetric and fusion is only occasional, features that allow us to rule out this diagnosis.

In conclusion, Cardinal Carlo de' Medici was affected by Klippel-Feil syndrome type III, a congenital anomaly of the cervical spine in which ankylosis of the cervical column is associated with the fusion of other elements in the thoracic and lumbar segments. There are also clear signs of tuberculosis of the cervical column (Pott's disease), thus confirming the information conveyed in historical documents.

The cardinal was also affected by severe ankylosing polyarthritis involving the large and small joints of the post-cranial skeleton. The differential diagnosis demonstrates the presence of rheumatoid arthritis (RA), as in another 16th century Italian case (19) with positivity for the DRB1*0101 allele that confers a genetic predisposition to European RA (28, 29).

These important findings clearly demonstrate the existence in the 16th century of an Old World variant of RA that follows the pattern of the treponematoses (11). We can presume that this disease was present in Europe before the discovery of America by Columbus in 1492.

Acknowledgements

We wish to thank Dr. Laura Cignoni of the National Research Council in Pisa for her help in the translation of this manuscript.

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