

The last battle of Alessandro Farnese (1545-1592): Some medical considerations regarding the health of the renaissance leader who changed Europe

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Abstract. *Background and aim:* Alessandro Farnese (1545-1592), 3rd Duke of Parma and Piacenza, one of the most important generals and politicians of his age. He died after a rapid deterioration of his health. The available documents testify that the Duke suffered for a long time from various health problems, such as jaundice, intestinal disorders, gout, dropsy but very little is known about the cause(s) of his death. The aim of this article is to offer for the first time a complete clinical interpretation of Alessandro Farnese's last months of life. *Methods:* A collection of descriptions of symptoms and signs described by his court physician and by the leading biographers of Farnese has been compiled. This collected medical evidence has been interpreted in the light of current medical knowledge, to obtain a final interpretation. *Results:* The results led us to consider liver diseases, neoplastic diseases (especially pancreas) and infectious diseases (including typhus and malaria) as causes or contributing causes of death. *Conclusions:* The accurate autopsy description, in association with the anamnestic information provided by the historical documents studied, suggests that Alessandro Farnese was a hepatopathic patient suffering from spontaneous bacterial peritonitis. In the pre-antibiotic era, the pathological organ alterations described certainly have at least contributed to making the infectious episode (that the autopsy describes of pulmonary origin) fatal. (www.actabiomedica.it)

Key words: Alessandro Farnese 3rd Duke of Parma and Piacenza, Renaissance, hepatosplenomegaly, autopsy, spontaneous bacterial peritonitis, history of medicine, pancreas.

Background

The Farnese family was an influential and noble dynasty of the Italian Renaissance, which ruled the Duchy of Parma and Piacenza from 1545 to 1731.

Several members of the family were major players in European politics, such as Cardinal Alessandro Farnese (1468-1549), who rose to the Papal throne, took the name of Pope Paul III and convened the Council of Trent in 1545; Elisabetta Farnese (1692-1766), Queen of Spain and wife of Philip V (1683-1746); and Alessandro Farnese (1545-1592), 3rd Duke of Parma

and Piacenza, one of the most important generals and politicians of his age (1).

The Duke was among the greatest leaders of the sixteenth century, thanks to his victories that shaped the political order of modern Europe for many years. Alessandro was the protagonist of several military campaigns, Lepanto at first and then Flanders, where he was governor and spent the last 15 years of his life. He was the key man of his uncle Philip II of Spain, with whom he had spent part of his youth, in the management of the war campaigns and conflicts with the subjects, proving to be also a brilliant and clever politician.

While in the service of Philip II of Spain, he acted as Governor General of the Netherlands (1578–92). He captured Antwerp in 1585, securing the southern Flanders for Spain.

His abilities became feared by all European rulers, including King Philip II of Spain himself, who eventually decided to dismiss him as governor. However, Alessandro Farnese died after a rapid deterioration of his health in Arras on December 3, 1592, before he knew the king's decision (2).

The circumstances of the death, contextualized in the historical-political framework, led some historians, over time, to suspect that Alessandro Farnese had been poisoned, without ever being able to prove it. Rumours of the period said that the Duke had been poisoned by Philip II but some historians, as the Cardinal Guido Bentivoglio (1577-1644) and Cesare Campana (1540-1606), thought they were unjustified (3). The available documents testify that the Duke suffered for a long time from various health problems, such as jaundice, intestinal disorders, gout, dropsy but very little is known about the cause(s) of his death (4).

Aim

The aim of this article is to offer for the first time a complete clinical interpretation of Alessandro Farnese's last months of life and demise after more than five hundred years from his death. Particular attention is here given to the symptoms and to description of the last months of the Duke, reported in detail by his court physician Ippolito Pennone (5).

The information that emerged from historical documents will be of fundamental support to the paleopathological studies that is being performed on the Duke's remains, examined during the recognition performed in 2019 (6).

Materials and methods

Pietro Fea, in his book entitled "Alessandro Farnese Duca di Parma, narrazione storica e militare" in 1886, drafted a complete biography of the protagonist, which includes notions of his military and private

life as well as references to his state of health. In his book he mentions two personalities of the time: Cardinal Guido Bentivoglio (1577-1644), a great historian of the 17th century with his main work "Della Guerra di Fiandra", and Cesare Campana (1540-1606), author of the book "Della Guerra di Fiandra fatta per difesa di religione da catholici re di Spagna Filippo II e Filippo III". The sources have been examined through philological, historical and medical analyses (2).

Moreover, the court physicians kept Alessandro's son and heir, Prince Ranuccio, who was in Italy, informed through letters which provide a diary of the Duke's illness (5).

The texts have been analysed in their original languages. A collection of descriptions of symptoms and signs has been compiled and this collected medical evidence has been interpreted in the light of current medical knowledge, to obtain a final interpretation.

Results

Up to the age of forty Alessandro proved to be a physically strong man, as described by the historian Bentivoglio. Although in his youth he was affected by illnesses, sometimes quite serious, his strong constitution was not affected. The author reports that in 1560, at the age of 15, he was struck by smallpox, in 1576 he was offended by smallpox-like lesion on one foot, and further illnesses struck him in 1561, 1569 and 1574.

The Duke suffered from gout. In Pietro Fea's book it is stated that the joints most affected by this pathology were the left knee, the right foot and the left hand (7).

Other members of his family like his uncle Cardinal Alessandro (1520-1589), his father Duke Ottavio (1524-1586) and his grandfather Duke Pier Luigi (1503-1547) also suffered from gout (8-10).

The Duke was well aware of this pathology and feared the disabling pains it entailed. For this reason, he refrained from consuming wine in his life (3). The way the wine was made and stored caused the levels of lead in the drink itself to be high. Lead can be responsible for a number of systemic diseases, including gout (11).

In Belgium, however, during the sieges of Maas-tricht and Antwerp (1584-1585), he fell ill with an infectious disease that caused him repeated tertian fever episodes. His army was also affected by these fevers during the stay (12).

Together this condition, however, also dropsy appeared which would have affect his state of health more substantially.

According to Bentivoglio and Campana, the reason for the Duke's illnesses originated partly from excessive drinking water for a long time, a remedy to fight gout, partly from the extreme hardships suffered during the siege of Antwerp, which resulted in a "stiffening" of the stomach and altered the liver giving rise to dropsy. According to the historian, therefore, Alessandro Farnese suffered from a liver disease that led to widespread oedemas (3).

These physical troubles had been one of the reasons that, during the winter of 1585-86, had induced the Duke to take a pause, and were becoming more serious from year to year.

Among the causes of deterioration in the health of the Duke, historians also consider the gunshot wound in his arm, which they say never healed completely. In 1592, during the exploration of the fortress of Caux, Caudebaec (Normandie), a small-town of 2500 inhabitants, "a blunderbuss shot at random from inside" injured his arm. Up to that moment the Duke had not suffered any kind of major wound in battle, apart from small bruises. The bullet went through the forearm passing between the ulna and radius and lodged itself in the carpus, and surgery was necessary to extract it. Pietro Fea reported that the surgeons, however, hesitated to perform the operation, and were forced by the Duke himself, as Alessandro Farnese's general condition appeared precarious. The oedemas were getting so bad that, according to the writer, he only had a few months to live. As soon as the arm wound was overcome, jaundice appeared, accompanied by frequent loss of consciousness, produced by the loss of blood (4).

The health conditions of the Duke precipitated in 1592, as witnessed by the letters that the court physician Ippolito Pennone sent to Ranuccio (5).

These letters, written in vernacular Italian, are rich in clinical information.

The first letter in chronological order, dated 22 August 1592, states that the Duke had been drinking Spa water for two months, with great benefit, but in August the doctor reported an important dysentery, which debilitated him greatly, and the appearance of erysipelas in one leg.

On the evening of 23 August, Farnese was trembling, had difficulty standing upright and appeared confused, but still managed to feed himself regularly. During the night he complained of abdominal pain in the periumbilical region, which resolved without any particular treatment. (*Sua Altezza incominciò a tremare, a non poter star in piedi et a parlar for di proposito. Con tutto ciò cenò assai bene. A mezzanotte mi chiamò et mi disse che sentiva un dolore intorno l'ombelico*).

The physician Pennone reported that the following day Alessandro Farnese was still trembling and had no thirst, almost as if to underline the exceptional nature of the event and suggest that he usually had polydipsia instead. He deteriorated until he became sleepy (*stette sonachioso et non sapeva parlar a proposito*).

On the morning of the 25th, Pennone administered two and a half drams of rhubarb to Farnese for purgative purposes, resulting in an immediate improvement in the Duke's condition, who became completely lucid again and could walk without trembling (*è stato talmente ben purgato che pare sù risuscitato et hora parla in bonissimo proposito, cammina, non trema, ha desinato con appetito et è allegrissimo conoscendo il pericolo in che è stato*).

In the same letter, the physician describes the Duke as "so thin that he looks like a skeleton", although he had regained his appetite.

The treatment recommended by Pennone led to an improvement in the Duke's state of health, which however lasted only a few days. On the 28th, indeed, he became confused and presented nausea and vomiting, so he lost his appetite. All symptoms resolved the next day, 29 August, after the administration of rhubarb (*subito ritornò a stare allegro et perseverò in tal miglioramento*).

The following night the Duke presented with severe diarrhoea, but despite this he felt strong. An important reference is to the colour of his face and sclerae, which appeared healthy, in contrast to the colour of his urine, which was sometimes citrine and sometimes

dark. (*Dice nondimeno Sua Altezza che si sente migliorare quanto alle forze, et gli pare di far carne, il color del viso, et degli occhi è bonissimo, ma le urine sono tuttavia grosse et cresiche d'un color citrino, et rare volte sono cotte*). He presented a fluctuating appetite as opposed to a persistent polydipsia (*L'appetito di mangiare hora c'è, hora no, quello del bere c'è sempre grandissimo*).

In his letter dated 9 September 1592, Pennone also attributed the fact that the Duke had a swollen, globular abdomen to the large consumption of water (*il ventre più pieno di flati del solito*). He also reports that the Duke later found benefit from bloodletting (*una fontanella nel braccio sinistro*) recommended by Pietro di Castro.

On 18 September, Antonio Salvi, another of Ranuccio's agents, reported that the Duke was suffering from diarrhoea both at night and during the day, described him as pale and with gout in his right foot, hand and left knee, but despite this he continued his training on horseback. On the 24th, Salvi himself reported an improvement, in particular oedemas seemed to be reduced, as well as joint pain (*il corpo gli si è andato restringendo, la podagra va cessando. Si può sperare che sia sfuggito ad ogni pericolo*).

On 26 September a new relapse reported by Salvi, in particular obnubilation and sensory changes (*travagliarlo la melanconia e frequenti deliquiù*) (7).

An improvement on 3 October was announced by the secretary Cosimo Masi, who reported that the patient only had a slight gout (7).

On 14 October, however, Antonio Salvi described the presence of widespread oedemas, which did not regress despite the therapy recommended by Spanish doctors (*il suo corpo era gonfio in varii posti, che prendeva certi farmachi suggeritigli da medici spagnuoli, ma che non progrediva in modo sensibile*) (7).

Finally, on the 15th, the physician Bartolomeo Simonetta warned Ranuccio about the good news on his father's health, who appeared almost fully recovered (*non credesse Ranuccio alle buone notizie che gli mandavano circa la salute del padre; travagliarlo si forte scioglimento, da non lasciar luogo ad illusioni*) (7).

The Duke lived another month and a half, but his time was coming. However, such was his fortitude that the Duke did not stop working day and night throughout the rest of the month.

On 8 November Pennone returned to describe the presence of declivous oedema, which the Duke tried to alleviate with compresses, and abdominal swelling (*la pancia è una volta più gonfia dell'altra, i piedi et le gambe si enfianno infino al ginocchio, la mattina stanno meglio*). The spleen is described as hard and swollen (*milza è tuttavia dura et gonfia*), often treated with tobacco ointment without any benefit. Pennone reported that cough also appeared which, forcing him to get up at least four times every night, disturbed the Duke's sleep (*Quattro giorni sono si è raffreddato, et gli è sopravvenuta una tosse assai grande, la quale con il levarsi al servitio almeno quattro volte ogni notte, le disturba un poco il dormire*). In this letter, which appears to be one of the most descriptive of Alessandro Farnese's state of health, Pennone reported that the Duke had diarrhoea. (*va il più delle volte humori liquidi, fetidi, et bertinezzi*) and regular diuresis, although his morning urine was concentrated (*Le urine della mezza notte sono ordinariamente citrine senza segno di cationi, quelle della mattina sono accete*). Poor appetite persisted, associated with polydipsia. (*L'appetito è poco, la sete è grande*). Pennone concluded his account by emphasising the Duke's great fortitude, but, despite this, he admitted his fears about the advanced state of his disease (*l'animo è grandissimo... ma le cose sono in stato che con questo viaggio di Francia che si prepara di fare in breve, di che temesi a molti et a me in particolare*).

On the night between 2 and 3 December 1592, as Pennone wrote in his penultimate letter to Ranuccio, after 28 hours of unconsciousness the Duke died. According to Pietro Fea, at the age of 47 years, three months and five days, he breathed his last when anasarca reached his heart (*l'idropisia aveva toccato il cuore*).

When it seemed he was getting better he got worse again, with diarrhoea, widespread oedemas, "melancholy" and delirium. Perhaps the belly alteration, which was feared disastrous, would have been his salvation. (*Quando sembrava che stesse migliorando tornava a peggiorare. Diarrea, edemi diffusi, melanconia e deliri. Forse il distemperamento di ventre, che si temeva funesto, sarebbe stato la sua salvezza.*) (7).

Jaundice, dropsy, gout, hardening of the spleen, pain of the wound never well healed were associated with gastric disturbances, diarrhoea and mood alterations. (*All' ittero, all' idropisia, alla podagra,*

all' indurimento della milza, al dolore della ferita mai ben rimarginata, si erano ancora aggiunte nell'infermo un'estrema debolezza di stomaco, un micidiale flusso di ventre e una cupa melanconia) (4).

A few hours after his death, an accurate autopsy was performed in which the examiner identified pneumonia as the probable cause of death, but the anatomopathological description leaves room for other hypotheses of overlapping, if not dominant, pathological conditions. The liver is described as tough and similar to a medium-sized melon (*il fegato schizoso et grosso come un mediocre melone*); the spleen is described as being hard and enlarged, similar in size to a large melon (*la milza similmente dura et grossa come un gran mellone*); "putrefied" mesenteric veins (*le vene mesaraiche tutte putrefatte*). The bowel is described as dark and full of gas, perhaps ischemic, (*gli interiori negri et pieni di vento*); in the abdominal cavity there is no gas or dispersed liquids, contrary to what was imagined by the dissectors (*nella cavità dell'abdomine non era né acqua né vento*). Abdominal organs, peritoneum, diaphragm are described as being embedded together (*il fegato, la milza, gli interiori, tutti, il peritoneo, l'omento, et il diafragma erano tutti insieme uniti et attaccati all'abdomine*)(5).

The autopsic investigation found kidneys, heart and brain without pathological anatomical alterations (*I rognoni erano buoni [...], il core era bellissimo, piccolissimo, sodo et ben formato, il cervello era intiero senza macula alcuna*). A month before his death the cough had appeared and at the autopsy his lungs were "intimately contaminated and full of putrelent matter" (*i polmoni erano intieramente contaminati et pieni di materia putrelente*), as in the case of massive bilateral pneumonia which was probably the ultimate cause of death. Infectious complications are in fact often the cause of death in weakened patients.

The autopsy finds "intestines niggers and full of wind" which could be evidence of transmural necrosis or, simply, congestion.

Discussion

These are the main symptoms and signs reported by the writings on Alessandro Farnese's health conditions. The clinical situation appears to

be characterized by all the traits of chronicity, with phases of remission, phases of relapse and, lastly, an irreversible decay.

Farnese's disease, while progressive, appears to show several phases of remission, during which, albeit with much effort, he continued to work. A remission of this sort can be explained in terms of that clinically known phenomenon whereby patients showing heart or hepatic failure manage to stay asymptomatic for long periods of time as they adjust their lifestyle and habits to their progressively impaired physiology, that is, to the limitations imposed on them by their disease.

From his physician's letters to his son Ranuccio and from few other documents we obtain precise information about his state of health, which we can interpret and summarise as derived from various pathological conditions, compatible with the autopsy report. In particular hepatosplenomegaly is non-specific and common to many diseases. Among the most frequent are cirrhosis of the liver, portal and/or splenic thrombosis, lymphoproliferative diseases, infectious diseases, like malaria or typhoid fever.

Cirrhosis

Many of the symptoms and signs presented by the Duke can be collected within the picture of cirrhosis of the liver (13). First of all, in the last months of the Duke's life, tremors, changes in mood, difficulty in expressing oneself, and somnolence recurred: these symptoms were resolved by purging the patient with rhubarb. The sennosides present in rhubarb extracts have been traditionally used as a laxative. The use of rhubarb was in fact beneficial for the patient, who returned lucid after evacuating (14).

These neurological alterations and their resolution with evacuation are characteristic of hepatic encephalopathy (15).

Intermittent jaundice, not associated with fever, suggests first of all a chronic liver disease in its phases of decompensation. The obstructive hypothesis seems to be less plausible in relation to the fact that the jaundice episodes were not accompanied, in the detailed description, by fever or abdominal pain, and seems to have been present for a long time .

Lack of appetite, progressive asthenia and thinness reveal a progressive picture that can be due both to a chronic and a neoplastic liver pathology.

Abdominal distension, in a view of ascites, could also be part of symptoms and signs linked to chronic hepatopathy, then thirst could be secondary to effective hypovolemia hypoalbuminemia related (13).

In addition, generalised oedemas, in the presence of a normal heart and kidneys, are attributable to a hepatic cause, as the historians of the time themselves hypothesize.

Chronic mesenteric ischemia associated with venous thrombosis of the abdominal vessels that can occur in case of liver cirrhosis could justify the diarrhoeal bowel of the Duke Farnese, with foul-smelling stools (16).

A further characteristic of chronic hepatopathy is that it remains silent for a long time, giving evidence of itself only in the decompensation phase. This would explain Alessandro Farnese's relatively good health and physical vigour, which quickly turned into the severe conditions that led to his death.

At the autopsy, the finding of hardening of the liver and spleen, which was also enlarged, without obvious focal lesions, seems to further support this hypothesis. In the same way, the description of the peritoneum and abdominal organ receptacle could represent adherent outcomes of recurrent spontaneous bacterial peritonitis (17). In this sense, the involvement of abdominal vessels with dark bowel could be interpreted as thrombotic, characteristic of splanchnic venous stasis during cirrhosis: portal and mesentery thrombosis ending in bowel ischemia.

Certainly the Duke was not a drinker, in fact he had deprived himself of wine for his whole life to avoid worsening his gout, so we exclude the alcoholic cause of cirrhosis. However, there are many causes of chronic hepatopathy: viral, autoimmune, genetic etc (13). We could exclude obstructive hepatopathies, such as primary sclerosing cholangitis, as there do not seem to be any colangitic episodes or itching in the Duke's life, which represent one of the main characteristics of this pathology (18). Also hemochromatosis and Wilson's disease should be excluded because there is no clear multisystemic involvement, which is instead typical of these diseases (19).

Pancreatic cancer

The gluing of the peritoneum and abdominal organs described could refer to peritoneal carcinosis. It is well known that this pathology is usually a secondary of other oncological pathologies, most frequently of ovaries, colon-rectum, stomach, pancreas (20).

All these organs are either absent in the Duke (for obvious gender reasons), or described as normal. The only one that is not described is the pancreas.

This is not to be considered as an oversight or an omission. In fact, the pancreas was not recognized as an organ separated from mesentery until the end of XVI sec. (21).

A possible pancreatic cancer is compatible with the Duke's thinness and his rapid decline. The abdominal picture described in the autopsy could depict a peritoneal carcinosis with the involvement of mesenteric vessels, described as "putrefied", as if they were invaded by neoplasia.

Diarrhoeal bowel of the Duke Farnese, with foul-smelling stools may be malabsorption consequent to pancreatic neoplasia and steatorrhea, or chronic mesenteric ischemia associated with venous thrombosis of the abdominal vessels that can both occur in case of abdominal neoplasia.

From the symptoms it is possible to distinguish the cancer of the pancreatic head from that which affects its body and tail.

The first has worsening obstructive jaundice among the onset symptoms.

The second is not characterized, at least initially, by jaundice. Instead, the onset of diabetes mellitus is more characteristic due to the destruction of the more concentrated pancreatic islets in the body and tail of the pancreas.

Considering the patient's remitting jaundice and some symptoms also attributable to diabetes, such as ketonuria, polydipsia and weight loss, the hypothesis of cancer of the body or tail of the pancreas is more likely.

The absence of free abdominal fluid during the autopsy, however, renders unlikely a neoplastic cause due to peritoneal carcinosis, since, in this case, the accumulation of ascites would have been progressive, without an improvement. (22-24).

Malaria or typhoid fever

Historians say that when Alessandro Farnese arrived in Flanders the marshy environment caused him serious feverish episodes (tertian fever).

It is well known that Flanders have been a malarial area until relatively recently (25).

The pathology hardly has a chronic course but its manifestations can last for years.

Malaria can also cause jaundice, as a consequence of haemolysis, especially during severe infection with *P. falciparum*, and the cretaceous urine. During malaria splenomegaly (described in the autopsy with the spleen of a size similar to a large melon) is common and, after many attacks, it may become fibrotic and hard or, in some patients, it tends to swell massively (tropical splenomegaly). Hepatomegaly usually accompanies splenomegaly. However, liver subversion (described as a small melon) does not appear to be compatible with this infectious disease as it does not lead to cirrhosis despite the fact that some plasmids, in particular *P. malariae* and *P. ovale*, can give hypnozoites in the liver. In general, liver failure is only observed in association with a concomitant viral hepatitis or following a serious infection with *P. falciparum*. Painful hepatomegaly with splenomegaly is common. It is therefore possible that malaria justifies some of the symptoms (26,27).

Typhoid is usually contracted by ingestion of food or water contaminated by fecal or urinary carriers excreting *S. enterica* serotype typhi. Typical course is about of 4 weeks: patients present fever, malaise, anorexia, nausea, abdominal discomfort (constipation or diarrhoea, hepatomegaly and splenomegaly) (28). There may be a history of intermittent confusion, and many patients have a characteristic apathetic behaviour. We find many of these signs and symptoms in the Duke. Typhoid induces systemic and local humoral and cellular immune responses, but these confer incomplete protection against relapse and reinfection. Relapse occurs in 5 to 10 percent of patients, usually two to three weeks after the resolution of fever, but this in any case could not explain the recurrence of symptoms over the years.

In our opinion, therefore, infectious pathologies, from which the Farnese undoubtedly suffered, most probably acted as a trigger or a background to other conditions.

Conclusions

As almost always happens, it is not possible to identify a single, certain cause of death of an individual in historical-medical retrospective diagnoses.

In the specific case of Alessandro Farnese, the rich historical documentation, both biographical and medical, allows to attest a rapid and progressive deterioration of his state of health.

The accurate autopsy description, in association with the anamnestic information provided by the historical documents studied, suggests that Alessandro Farnese was a hepatopathic patient suffering from spontaneous bacterial peritonitis.

In the pre-antibiotic era, the pathological organ alterations described certainly have at least contributed to making the infectious episode (that the autopsy describes of pulmonary origin) fatal.

The gunshot wound that affected Alessandro Farnese's arm for some historians represented the main cause of the physical decay that led to his death.

Pennone's autopsy never mentions the Duke's arms. Research on recently unearthed bone findings may provide further details to complete the clinical picture.

However, we think that this study will help future paleopathological research on the Duke's remains, providing an overall clinical information and anatomical description of organs no longer examinable.

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