The first reported medieval judicial autopsy on Azzolino Degli Onesti: poisoning or Budd-Chiari syndrome?

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Abstract. The practice of autopsy on human corpses performed to increase anatomical and physio-pathological knowledge has been reported since ancient times, even if it has often been opposed by medical theories and religious beliefs. The first officially reported autopsy in Italy was described by Salimbene in 1286 during an epidemic that involved hens and human beings. The development of medico-legal practice on corpses dates back to the Middle Ages in Bologna, the city that boasted the most advanced medical and legal faculties of the time. Some of these autopsy reports have come down to our times and provide interesting information on the medico-legal procedures of the time. A significant example is the case of Azzolino degli Onesti: it was suspected that he died of poisoning, but the interpretation of the autopsy report based on current medical knowledge may suggest different conclusions.

Key words: story of autopsy, Budd-Chiari syndrome

A brief history of autopsy from ancient times to the Middle Ages

Not too much information is available about the practice of dissecting human bodies in ancient times, probably because human diseases, according to the animistic concepts of the time, were considered the consequence of the will of gods or some sort of spiritual forces, that stand above the merely "natural" order of things, making completely useless the pathological-anatomical investigation on persons who died of natural disease (1).

An important exception was represented by Ancient Egyptians (2,3) who did not forbid the dissection of human bodies, as demonstrated by the Edwin Smith Papyrus, which contains some detailed anatomical descriptions, especially of the brain.

In Alexandria, in the 3rd century BC, Ptolemy I and his son Ptolemy II allowed the practice of dissection providing the corpses of criminals for that purpose and, according to Plinius, were present at the dissections.

Herophilus (335-280 BC) was the first physician to systematically perform scientific dissection of human corpses and his anatomic and physiologic discoveries were phenomenal for the time (4,5), such as the functional differences between arteries and veins and between sensory and motor nerves and the thorough description of the cerebrum, cerebellum, and the meninges, the liver, the pancreas, the prostate, the heart valves and the eye, describing and naming its four parts as cornea, retina, choroid and iris; he was the first to recognize that testicles produce spermatozoa. About a generation later, Erasistratus (ca 310-250 B.C.) carried out dissections and made observations concerning the effects of diseases.

The discoveries of Herophilus and Erasistratus provided new insights and additions to the theory of Hippocrates (460-370 BC), who firstly tried to freeing medicine from mysticism and magic. On the other hand, they were accused by some ancient historical writers of having performed human vivisection; Celsius wrote (6): "*They procured criminals out of prison by royal permission, and dissecting them alive, contemplated, while they were yet breathing, the parts which nature had before concealed*". However, this terrible accusation was not confirmed, and it is important to notice, according to Dobson (7), that Galen, who possessed Herophilus

and Erasistratus original writings in their entirety, never makes mention of either of them ever performing vivisection.

Human cadaveric dissection was almost completely abandoned for many centuries after Herophilus' death, probably because of the success of the Empiricists, who specifically argued that organs in the dead undergo alteration and hence are so different from those in the living that it is useless to observe them (8).

It is unclear if human dissections were performed during the domination of the Roman Empire (many paintings suggest the presence of the Roman Emperor Nero at the "autopsy" of his mother Agrippina (9)), whereas there is enough evidence that autopsies were performed in Byzantine time (10).

It was not until the twelfth century that the first written reference to autopsies appeared. The British monk and historian William of Malmesbury reported in his chronicle Gesta Regum Anglorum (Deeds of the Kings of the English, 1125 AD) that in 1111 the Norwegian King Sigmurd I Magnusson (the Crusader) on his return from Jerusalem had one of his many dead soldiers eviscerated in Constantinople to compare his liver changes with those of a pig liver kept in the same wine the soldier had been drinking (11).

In medieval England, Germany and France human dissection was limited to the process of "division of the corpse", a practice that consisted either of the evisceration of the body in preparation for a state funeral, or a complete dismemberment (12). The latter was performed on the bodies of Saints and allowed several religious local communities to have access to a part of such illustrious people (13).

As far as we know, the first recorded case in Italy of a human body dissection, probably limited to the thorax to examine the heart, performed by un unnamed physician from Cremona for pathological-anatomical and not judicial purpose, dates from 1286, for the purposes of investigating the origin of a mysterious epidemic spread in central-northern Italy that killed hens and human beings. According to the chronicler Salimbene (14,15), "*there was in Cremona, Piacenza, Parma, Reggio, and many other Italian cities and bishoprics, a great mortality among both humans and hens. And in Cremona, one woman lost forty-eight hens in a very short time. A certain physician had some of the [hens] opened and found [that] there was a vesicular aposteme on the tip of each hen's heart. He also had a dead man opened and found the same thing*", such a suggestive coincidence that people were warned to avoid eating chicken and eggs.

It is wrongly believed that human dissections were strongly prohibited by the Church in the Middle Ages, but it is not true (16). A reason for this mistake probably derives from the bull *Detestande feritatis* issued by Pope Boniface VIII (the archenemy of Dante Alighieri) on 27 September 1299, which was soon incorporated into the canonical collection *Extravagantes communes* and thus became part of the Church's law regulating burial practices. Actually, the aim of the bull was not the anatomical dissection for medical purpose, but the practice of disembowelling and severing cadavers, especially those of nobles who died far from their native place (17), in order to send or carry their remains to the place reserved for interment.

The favourable orientation of the Church towards human autopsy was indirectly confirmed by Pope Innocent III, who requested such examination to be carried out to provide evidential basis for a papal verdict in two cases where a chaplain and a bishop were supposed to be guilty of murder (18).

By the early fourteenth century, medical professors at the university of Bologna (Ruggiero Frugardi, Taddeo Alderotti, Guglielmo da Saliceto) introduced the practice of dissecting human corpses into the study and teaching of anatomy, for the first time since the early Hellenistic period, but it was thanks to Mondino Liuzzi's famous "Anothomia", the first medieval treatise on the dissection of the human body (1316), that human dissection obtained the role of a knowledge instrument to a certain extent (19).

Over the course of the fourteenth century, both dissection and autopsy spread rapidly in the cities of northern and central Italy, where they were taken up enthusiastically not only by medical faculties, but also by municipal colleges of physicians and surgeons (20).

The development of medico-legal practice in Bologna in the Middle Ages

The practice of autopsy to determine the cause of death was quickly transferred from a public health to a forensic context in Bologna, the city that boasted the most advanced medical and legal faculties of the time.

Singer (21) pointed out that the University of Bologna was largely controlled by the law faculty, who would probably seek autopsies to help solve legal problems rather than to promote medical knowledge.

From a legislative point of view, the first references to the involvement of doctors in criminal proceedings can be found in the communal statutory collections of Bologna, given that at that time there was not a legal system valid throughout Italy. The first Statute, edited by Loderingo degli Andalò e Catalano (22) on 5 February 1265, was later updated and modified in 1288. It established that the *iudex potestatis ad maleficia*, while investigating a murder case, had to appoint two (or more) doctors to examine the body in order to assess the number of deadly wounds and establish the maximum number of those who were potentially to be accused. The Statute explicitly established that doctors were to be chosen at random among the "*most knowledgeable and worthy [men] in the science of surgery and medicine*". They had to be at least 40 years old and had lived in the city of Bologna for at least 10 years. Besides, they had to possess assets worth at least 100 lire of Bolognini, so that they could not be susceptible to corruption.

The selected doctors were required to swear an oath and were sent, accompanied by a notary, to examine the body of the deceased. After they finished the examination, they had to draft a report (generally hand-written by the notary) about the results of their inspection. The 1335 Statute established also that the offended party could request a medical investigation even before the start of the legal action and the expert doctors could be charged of investigating not only in case of death caused by injury, but also for death due to strangling, suffocation, and poisoning.

These medico-legal reports were very concise and provided very little information about the procedure. In the beginning, the medical-legal investigation was limited to an external inspection of the dead body, while dissections of the corpse for forensic purpose date from the 14th century, and the first of them being officially reported was that of Azzolino degli Onesti.

The autopsy of Azzolino degli Onesti

On 25 February 1302, Azzolino degli Onesti died suddenly on his bed. The day before his doctor, Barufaldini, went to visit him and was informed by the wife that Azzolino had been ill for a few days. The doctor suspected that Azzolino had the intestine infested by worms so advised his relatives to prepare a poultice based on wormwood, lupins and vinegar and spread it on his abdomen.

After the death, the *Iudex ad maleficia* suspected that Azzolino had been poisoned and commissioned five doctors, the two physicians Bartolomeo da Varignana (a lecturer at the University) and Giacomo Rolladini and three surgeons (Tommaso Grinci, Giovanni da Brescia, and Angelo Pacedelli), to perform the autopsy on the body with the aim of confirming or excluding the suspicion.

The commission concluded that: "*Azzolino did not die of poisoning; it was more likely and certainly an excess of blood that gathered in the large vein referred to as the venae cavae and in the veins of the liver around it, which blocked the flow of the spirit in the whole body and consequently led to complete mortification, or in other words, the extinction of heat generated from within*" (23).

Unfortunately, the short autopsy report did not provide any description of the abdominal viscera and, in particular, of the liver, which would have been of particular importance in attempting to identify, on the basis of current medical knowledge, the true cause of Azzolino's death. Even with these limitations, the occlusion of the vena cava and hepatic veins by an excess of blood described in the report is strongly indicative of the possibility that Azzolino suffered from Budd-Chiari syndrome (BCS), an uncommon disorder that affects 1/100,000 of the general population worldwide, characterized by the obstruction of the hepatic venous outflow (24).

In the past, the term Budd-Chiari syndrome was used to designate various conditions, a fact that was occasionally misleading, so the development of the studies of this pathology through the decades is of particular interest (25).

This disease was firstly described in 1845 by George Budd, who commented on three patients with obstruction of hepatic veins (26). Two patients had multiple liver abscesses involving one of the hepatic veins, with resulting thrombosis secondary to sepsis, whereas the third patient, who was addicted to alcoholism, developed adhesive pericarditis and peritonitis and unusual "adhesive" inflammation of the liver.

In 1867, Rosenblatt considered the obstruction of hepatic veins as the result of an interstitial hepatitis occurred during the foetal period (27); in this hypothesis, the distortion of the liver architecture as a result of deposition of fibrosis was associated with the development of an irregular and stenotic anastomosis between the hepatic veins and the inferior vena cava, causing the obstruction.

In 1898 a second case series was published by Hans Chiari: as pathologist in Prague, he examined three patients with hepatic veins' thrombosis (28) and observed that their livers were significantly congested and necrotic, with congestion of the porto-mesenteric circulation and large volume ascites, while histology showed minimal adventitial reaction without any significant perivascular involvement. He pointed out that this disease might rapidly led to death and named it '*phlebitis obliterans*". Thrombosis was considered a complication of an endo-phlebitis process, occurring in the context of syphilis, but this hypothesis was not confirmed in the following years. Nevertheless, this description is a cornerstone in the study of BCS because it was the first report including clinical and pathophysiological correlations.

In the following decades, several hypotheses about the aetiology of BCS were proposed. Moore, in 1902, described the occlusion of hepatic veins as the result of a fibrotic process triggered by an unknown factor. Kretz, in 1902, shifted the attention to the vascular anatomy: he believed that the mechanical stress with micro traumatic events of hepatic veins, that hold up the liver in the abdomen (such as in case of chronic cough), might be the cause of obstruction in predisposed patients. In 1912, Thompson & Turnbull criticized the theory proposed by Chiari regarding the endo-phlebitis: they thought the upstream event was the thrombosis itself while the inflammatory changes occurring in the walls of hepatic veins were seen as a secondary phenomenon, basing also on the fact that obstruction of the hepatic veins was frequently located next to the ostia, and there was no reasonable explanation about why a generalized process such as endo-phlebitis should have preferred this location; the 'stasis of blood flow' at this site was recognized among risk factors for venous thromboembolic complications.

Few years later, the common coexistence of haematological diseases and BCS was reported although the pathophysiological role of thrombophilia associated with such conditions was not properly recognized. In 1929, Oppheinemer reported a clinical case of a young woman affected by polycythaemia vera who acutely developed ascites and jaundice; the post-mortem examination showed severe congestion of the liver and hepatic veins thrombosis (29). In the following years, other reports described an association between haematological disorders, rheumatologic, autoimmune diseases, and thrombosis of hepatic veins as recurrent autoptic manifestation.

In most of these conditions, patients were young, previously healthy, presenting with acute liver failure and the onset of symptoms was followed by death in most of the cases.

In the early 1900s, the distinction between 'primary' and 'secondary' forms of BCS began to take shape, thanks to the work of Kelsey and Comfort (30). In their autoptic population they were able to identify 20 patients with hepatic veins thrombosis: in 16 of them, the occlusion was accidentally found, in the others, it was considered to be the cause of death. Of these four, two were defined as 'secondary': in one patient a fibrosarcoma was narrowing the inferior vena cava, whereas in the other, there was a neoplastic thrombus within the lumen of the hepatic veins. In the other two, no cause was found, so the thrombosis was considered as primary. From a clinical point of view, Thompson & Turnbull in 1912 first identified two modes of presentation with different prognosis and outcome: 'acute' and 'chronic'. In the chronic form the morbid manifestations appear gradually, and the illness lasts from 1 to 6 months, whereas in the acute form the symptoms develop with rapidity and death supervenes in a few days. The distinctive factor between the two forms was identified in the time-development of the thrombosis.

In 1959, Parker published the very first 'modern' paper (31), in which he included 254 patients with hepatic veins occlusion (18 cases from his own series and 236 that had previously reported). The disease occurred with similar frequency in men and women, mainly in young adults. He described three forms according to time-development of the disease: acute, sub-acute

and chronic, with a wide range in terms of duration of symptoms (from 2 days to 23 years). Most of the patients died because of hepatic and multiorgan failure. A characteristic of thrombosis is the concomitant presence of other lesions in the liver: BCS syndrome is a well-recognized cause of post-sinusoidal portal hypertension. Parker et al first reported the presence of portal hypertension stigmata: splenomegaly (25%), porto-systemic spontaneous shunts (10%) and portal vein thrombosis (PVT) (20%).

Recently, however, international panels have agreed that Budd-Chiari syndrome (BCS) be used as an eponym for hepatic venous outflow tract obstruction, regardless of the level or the mechanism of obstruction (32,33,34).

The obstruction may be anywhere along the venous course from the hepatic venules to the junction of the inferior vena cava (IVC) to the right atrium and it leads to hepatic congestion and ischemic necrosis of hepatocytes. Severity depends on the speed of onset and the extent of the obstruction (35).

Obstructions are generally caused by thrombosis (primary BCS), whereas secondary BCS results from tumour invasion into the lumen or compression of the vein by an expansive lesion.

Blockage of two or more major hepatic veins is necessary for clinical disease: it increases the sinusoidal pressure and reduces sinusoidal blood flow resulting in liver congestion, right upper the quadrant pain and ascites. Portal pressure increases and perfusion of the liver via portal vein is decreased, the combined effect of these changes in hepatic circulation resulting in hypoxic damage of hepatocytes.

The symptoms of BCS are related to hepatic insufficiency and portal hypertension and consist in pain in the upper abdomen, ascites, jaundice, enlarged and tender liver and spleen, oesophageal bleeding by varices, edema of the legs, hepatic encephalopathy, fatigue (extreme tiredness).

Diagnosis can usually be established by non-invasive means through imaging of the hepatic veins and the inferior vena cava (Doppler ultrasound, tomodensitometry and MRI).

The natural course of the disease is very severe (less than 10% of patients survive for more than 3 years without treatment). Usually, portal hypertension and ascites evolve in chronic form but rarely the BCS has a fulminant course from massive hepatocellular (36).

Obviously, the concise autopsy report does not allow to speculate on the exact cause of death, but, excluding poisoning and referring to a natural pathology, the possibility that Azzolino died of BCS represents a valid hypothesis on the basis of the updated medical knowledge.

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