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Karl Stellwag von Carion (1823-1904) and his studies on clinical and pathological anatomy of ocular cancer

Konstantinos Laios¹, Efstathia Lagiou², Maria Piagkou³, George Kitsos⁴, Marilita M. Moschos^{5,6}¹Medical School, National and Kapodistrian University of Athens²Medical School, University of Patras³Department of Anatomy, Medical School, National and Kapodistrian University of Athens⁴Department of Ophthalmology, Medical School, University of Ioannina⁵1st Department of Ophthalmology, Medical School, National and Kapodistrian University of Athens⁶Biomedical Research Foundation, Academy of Athens

Abstract

Karl Stellwag von Carion (1823-1904) was a very important figure of European ophthalmology during the 19th century. Besides his other contributions in ophthalmology such as 'Stellwag sign', coining the term 'ectopia lentis' for lens dislocation and fundamental studies on glaucoma, refraction, accommodation and light polarization, his studies on ocular cancer were very significant but not highlighted by modern research.

Key words

Karl Stellwag von Carion, ocular cancer, glioma, melanoma, pathological anatomy of ocular diseases.

Introduction

Karl Stellwag von Carion (1823-1904) was born in Vienna. He studied medicine in Prague and Vienna and in 1847 he received his doctoral degree in medicine and, the same year, his license as surgeon in Vienna. In 1847 he started his internship in ophthalmology in Vienna General Hospital until 1851. In 1854 he was elected Dozent (lecture) in ophthalmology at the university of Vienna and Josephs-Akademie and in 1857 he received the title of 'Professor extraordinarius' of ophthalmology in the same university. Finally, in 1858 he became Full Professor of Ophthalmology at the university of Vienna (Pagel, 1901).

In the history of ophthalmology he is well known from 'Stellwag sign' (a sign of infrequent or incomplete blinking associated with exophthalmos) and coining the term 'ectopia lentis' for lens dislocation. Very important were his studies on glaucoma, on refraction, on accommodation and light polarization (Pagel, 1901). Nevertheless, his studies on ocular cancer, although very important in the history of the study of this disease, were over passed by his other contributions in ophthalmology. The clinical and pathological studies on ocular cancer made by Stellwag mark the new pathway of the study of this disease which was followed by the physicians in the middle of 19th century leading ocular oncology to change the theories and descrip-

* Corresponding author. E-mail: konstlaios@gmail.com

tions of the disease made until then. The new ideas about this disease were described and analyzed in a simple but accurate way pointing the new achievements in ocular pathology which were a breakthrough for that time.

Clinical and pathological anatomy of ocular cancer by Karl Stellwag von Carion

We can learn Stellwag's ideas about ocular cancer from his three most important treatises on the theme, *Die Ophthalmologie vom naturwissenschaftlichen Standpunkte aus* (1853) (Ophthalmology from the scientific point of view) (Stellwag, 1853), *Lehrbuch der praktischen Augenheilkunde* (1862) (Textbook of practical ophthalmology) (Stellwag, 1870; see cover at <https://archive.org/details/lehrbuchderprak02carigoog>) and, with the collaboration of Carl Wedl (1815-1891) and Carl von Rokitansky (1804-1878), *Atlas der pathologischen Histologie des Auges* (1861) (Atlas of pathological histology of the eye; Wedl and Stellwag, 1861; see <https://archive.org/details/b21284799>).

Stellwag highlighted the key characteristics that must be present in order to classify as malignant an ocular neoplasm. He emphasized that, unlike in the past, malignancy should not generally be defined as a tumor that develops too fast or presents lymphogenous or hematogenous metastases or even is difficult to be removed and recurs as a rule after excision. Instead, he considered that the key element in identifying malignancy was whether cancer cells resembled their maternal cell (differentiation) and whether they are found between another tissue with different characteristics, such as for example when epithelial cells are localized in connective or cartilaginous tissue. He underlined also that malignancy was severe in the presence of mucus cells in the cytoplasm or in cases with many mitoses. These general characteristics of malignancy illustrated a completely different way of thinking and approaching cancer, not only ocular one but in general (Stellwag, 1870).

He considered as ocular carcinoma a malignant tumor consisting of epithelial cells with acinar arrangement. He noted that these cells could be pigmented in the cytoplasm and give the impression that they were melanocytes. He pointed out that it was difficult their distinction from melanocytes when they were spindle-shaped or small and round or giant. However the biological behaviour and the acinar arrangement, were characteristic elements of their identity. According to this physician this type of ocular cancer was of exceptional malignancy with metastatic potential through lymph. He also believed that this type of ocular cancer could occur in every ocular tunics or other anatomical structure of the eye, although it was emphasized that it was more difficult to develop intraocularly, arguing that never before such a malignancy had been seen. He added also that malignant cells of ocular carcinomas were often found in sarcomas (Stellwag, 1870).

Regarding ocular sarcoma he thought that it had a variety of appearance, therefore it was identified with many forms of cancer, such as fibroplasia, myeloid cancer, melanosarcoma, carcinoma and adiposarcoma, for example. Due to the fact that its structure resembled various types of connective tissue, it was characterized as fibromatous, mucous, glioma, melano-, chondro- and osteosarcoma. Sarcoma cells derived from connective tissue cells in hypertrophic state. The ligaments were different from those seen in the carcinoma. The cytoplasm was reduced in amount. If pigmented cytoplasm was observed, then the tumor was characterized as melanosar-

coma. The cells, apart from a great number of mitoses, presented a spindle, spine, or circular shape and larger or even giant cells could appear. They also had a large nucleus or many nuclei. All sarcomas were thought to have rich neovascularization, which allowed the rapid growth of the tumor. Small cell sarcomas was considered the most deadly. The malignant character of sarcoma occurred mostly years after first appearance. Sarcomas were believed to present in every ocular tunic, although they were more often seen in orbit. They were more frequent in adults and did not easily present ulcers (Wedl and Stellwag, 1861).

Stellwag did not deal in depth with ocular melanoma. He stated that this type of ocular cancer could be distinguished by the pigmentation. He believed that they could arise from iris, conjunctiva, cornea, orbit and eyelids (Stellwag, 1870).

Another type of malignant neoplasm in the eye that was analyzed by this physician was retinal glioma. During his era it was not yet recognized as retinoblastoma, as it was in the early 20th century (Kivelä, 2009). Following Rudolf Ludwig Carl Virchow (1821-1902) he also accepted that this tumor originated from neuroglia (Virchow, 1863). He listed it as a soft cancer according its macroscopic characteristics. From microscopic analysis he suggested that the tumor consisted of very small round cells with large circular nuclei that were quite close to the cell surface. Within the cytoplasm he stressed that fibrils were distinguished, while fatty degeneration was observed during the expansion of this neoplasia. He pointed that this type of ocular cancer could arise from all layers of the retina, expanding even on the optic nerve and developing intraocularly as well destroying gradually the rest of ocular tunics, not excluding the orbit. He also reported that in one fifth of cases there was an attack to the other eye, either due to the expansion of the disease through the optic chiasm or through the brain (Wedl and Stellwag, 1861). The disease was classified as a children's disease, because no patients older than twelve years were recorded. It is worth noting that the physician did not present any evidence about the causes of this disease and did not relate cachexia or any type of injuries to the onset of this pathological condition.

The clinical signs either of exo- or intraocular tumors were summarized by Stellwag as follows: he underlined the presence of exophthalmoses in the majority of malignant ocular tumors, the difficulty in the movement of the bulbar or the iris due to the pressure of the tumor and visual disorders or blindness. As for glioma (retinoblastoma) he indicated the formation of opacity at the fundus and the whitish or yellow spots found in fundus during ophthalmoscopy. The only effective treatment he proposed for every type of ocular cancer was tumor resection or enucleation depending on the size and the expansion of the malignant tumor (Stellwag, 1870).

Discussion

Ancient Greek physicians for the first time in medical history introduced and defined cancer as a special disease (Leven, 2004). But cancer in Greek antiquity had a different context than that of modern medicine. For ancient physicians almost every severe and incurable inflammation with ulcers presenting in any human organ was diagnosed as cancer. These fundamental characteristic were assumed also for similar conditions presenting in the eye. Nevertheless, the clinical signs of ocular cancer in

antiquity were more specified. According ancient Greek physicians such as Rufus of Ephesus (1st - 2nd century AD), Soranus of Ephesus (2nd half of 1st - 1st quarter of 2nd century AD), Galen (1st - 2nd century. AD), Xenophon of Kos (1st century AD), Demosthenes Philalithis (1st half of 1st century AD) and Aretaeus of Cappadocia (2nd of 3rd or 4th century AD), ocular cancer presented with incurable cancerous ulcers, outflow of liquid (humor, mainly melancholic bile) from these wounds, strong pain, stiffness in the organ, defects of vision up to blindness, edema, exophthalmos and tumors that could appear in the bulb, orbit or eyelids. It was also considered that there were mainly two types of the disease, the soft and the 'hard' one, so-called skirrhus cancer; many patients presented with cachexia and the disease affected more often people of mature age and especially menopausal women who had suffered in the past chronic ocular inflammation (Karamperopoulos, 2004).

These doctrines about ocular cancer were adopted by Roman physicians, as Cassius Felix (5th century AD), Scribonius Largus (1-50 AD) and Marcellus Burdigalensis (5th century AD), Encyclopaedists, as Aulus Cornelius Celsus (25 BC - 50 AD) and Gaius Plinius Secundus (23-79 AD) (Pioreschi, 1998), Byzantine physicians, as Alexander of Tralles (525-605 AD), Johannes Zacharias Actuarius (1275-1328), Michael (born Constantine) Psellos (1018-1078) and Theophanes or Chrisovalantes Nonnus (10th c. AD) (Pioreschi, 2001), and Arab physician, as Abu'l-Qūsim Ammar ibn Ali al-Mawsili (9th - 10th century AD), Alī ibn 'Īsā al-Kahhal (940-1010), 'Ali ibn al-'Abbas al-Majusi (?-982/994) and Sadaqa ibn Ibrahim al-Misri as-Sadili (2nd half 14th century AD) (Hirschberg 1904). The doctrines passed to Medieval Europe through the later ones, as we learn from the medical writings of Christianus Toletanus (12th century AD), Benevenutus Grassus (12th - 13th century AD), Pope John XXI (Petrus Hispanus) (1205-1277), Henri de Mondeville (1260-1316) and Guy de Chauliac (1300-1368) (Hirschberg, 1908).

Ancient medical doctrines were disputed during Renaissance and Baroque age (Arrington and Mart-Ibanez, 1959). The beginning of questioning the authority of the ancient Greek physicians is marked by the challenging of anatomy doctrines and especially those who had been taught by Galen. Now under the anatomical research on human corpses, especially those of Leonardo Da Vinci (1452-1519) (O'Malley et al., 1952) and mainly those of Andreas Vesalius (1514-1564) (Vesalius, 1543), it was clear that the medical principles of the past could not be confirmed by scientific research.

Thus, the beliefs of the past began to crumble and the whole medicine was now under new research. However, the methodological tools of the time did not allow physicians to correctly understand physiology and pathophysiology of the human body, which will be achieved gradually from 18th century.

Regarding ocular cancer, the progress of the study is parallel with the progression of the study on cancer in general. Much progress was achieved during 19th century, when it the science of pathology was established with the introduction of the use of more powerful microscopes.

Having in mind the above we can understand why from the 16th and 17th centuries the works about nature and causes of ocular cancer underwent gradual reduction in number except those concerning symptomatology of ocular cancer, as we particularly observe it in the work of Leonhart Fuchs (1501-1566) (Fuchs, 1539) and Jacques Guillemeau (1550-1613) (Guillemeau, 1585).

Thus, comparing the work in the first half of this century of Antoine Maître-Jan (1650-1725), where there is a slight reference to the body humors as a cause of ocular

cancer showing signs of slightest attachment to the past (Maître-Jan, 1740), with that of Antonio Scarpa (1747-1832) in the early 18th century, the differences are great (Scarpa, 1816). Now the past only survives in the naming of ocular cancer, while detailed description of symptoms, clinical behavior and attempt to recognize the causes of the disease - linked at the time to microbiology - were the central elements of disease study. Antonio Scarpa's study on the theme is the hub and the bridge to the scientific investigation on this disease which blossomed the next century. The 19th century was the one to mark the beginning and establish the foundations of the scientific study and treatment of ocular cancer, as required by modern medicine. A key point of this fundamental change in 19th century was the establishing of the science of pathology.

Giovanni Battista Morgagni (1682-1771) is considered the founder of pathology. In his monumental five-volume work entitled, *De sedibus, et causis morborum per anatomicen indagatis libri quinque* (Five-volume study of the sites and causes of diseases analyzed through anatomy), attempted to investigate the characteristics of tissues in various diseases (Morgagni 1761). But, due to the facts that the technological development of the microscope was not such as to produce key results and that at that time the knowledge in medicine in general did not had an entirely scientific character yet, the goal was achieved a century later when Rudolf Ludwig Carl Virchow published his monumental work entitled *Die Cellularpathologie in ihrer Begründung auf physiologische und pathologische Gewebelehre* (Cellular pathology in its basis on physiological and pathological tissue theory), with which he not only placed the base of the modern study of pathology, but also overturned the established ideas on cancer indicating that one cell begets the other (*Omnis cellula e cellula*) and opening new pathways to cancer research in general (Virchow, 1858).

Virchow's ideas was followed by the majority of the physicians that time. His findings on cancer had been the final blow to the mistaken and virtually unscientific views about the cancer of the ancient past, which had been in question since two centuries earlier. Despite the new and correct scientific evidence, the road would be very long for deep understanding cancer, since there will be several mistakes, as modern medicine recognizes today, in the theories about cancer expressed from 19th century and later. But there was the substantial difference that the new theories were not accepted unaccountably but the researchers tried to support them with arguments based on the new scientific discoveries.

This was the historical and scientific background on the theories of cancer which was also applied to the study of ocular cancer. Having in mind this progress of scientific research in medicine and the establishment of pathology as a new field of medicine, we can now understand better the achievements and contribution of Stellwag in the study of ocular cancer.

Stellwag's studies on ophthalmic diseases and consequently ocular cancer constitute a milestone in the history of the study of this disease, because they mark the passage into the modern medical approach to these pathological conditions. With his writings, the change in the approach to interpret ocular cancer is obvious, so that experience could then be combined with modern scientific observation, which was the result of a multifaceted approach. The physicians from the mid 19th century were not satisfied with the interpretative propositions of the past centuries and wished more complete hypotheses and theories, which could correspond to the interpretive problems that arose since pathology shed new light on the pathological mechanism of ocular cancer.

From his study *Die Ophthalmologie vom naturwissenschaftlichen Standpunkte aus*, already from the title we can see a new perspective in the approach to ophthalmology. The title demonstrates that the analysis of ophthalmic diseases will now be based on scientific arguments resulting from the findings of the medical science of the time. Thus, in this book there is an integrated approach to ophthalmology, where ocular anatomy and physiology are presented simultaneously with pathology and pathophysiology of ophthalmic diseases, in every anatomical part of this organ. This study intended to demonstrate the multidimensional nature of ocular disease, so that the empirical approach as seen in earlier treatises was no more enough.

This work is quite theoretical and introduces the reader to the scientific research of the time. It did not have the character of an ophthalmology textbook that would help the physician in his daily work, although his value was great for the theoretical and research part of ophthalmology.

Therefore Stellwag wrote a separate study having the character of a manual of ophthalmology, which would be useful for the clinical and surgical part of ophthalmology. However, in this work he preserved the principles he relied on in the previous one, pointing out, in spite of its most practical character, that the physician should investigate and approach a disease by demonstrating its essential characteristics of pathophysiology and pathological anatomy. This book was entitled *Lehrbuch der praktischen Augenheilkunde*. It was very popular at the time not only because it had many editions, but because it had many translations, which in turn had also many editions also especially in America (Stellwag, 1873). In this work he analyzed ocular cancer, for which the basis of pathological anatomy had already been developed in the atlas of pathology of the eye that Stellwag published in 1861 in collaboration with Weld and Rokitansky, entitled *Atlas der pathologischen Histologie des Auges*.

Regarding ocular cancer Stellwag focused especially on the characteristics of the cancerous cells and their pathognomonic features, which were now the basis for the diagnosis of ocular cancer and the identification of each type of this disease. The atlas of pathological anatomy of ocular disease which he wrote with Weld and Rokitansky was the first atlas of ocular pathology in history where ocular cancer was analyzed in every detail and presented with its special characteristics in the ocular tunic or other anatomical part of the eye where it could develop. The first atlas of ocular pathology in history - published in 1808 by James Wardrop (1782–1869) and entitled *The morbid anatomy of the human eye* (Wardrop, 1834) - barely describes a malignant ulcer in the eyelids, a similar one in iris and a tumor probably also malignant of the optic nerve, but this representation was changed by the atlas of Stellwag, Weld and Rokitansky, where ocular cancer received special attention. Stellwag's atlas was also the prototype for the similar one written by Siegmund Ginsberg (1867-1942) and published many years later, in 1903.

Stellwag followed the ideas on retinoblastoma of his era, therefore he used also the term glioma, as this disease was called at the time. He did not deal much with ocular melanoma, because at that time this type of ocular cancer was confusing for physicians since, due to pigment in the cells, they could not be accurate in evaluating whether these tumors were benign or malignant. Stellwag tended to believe that this type of tumor was malignant, probably he would have needed to examine more cases in order to conclude unambiguously for its malignant character. On the other hand he was also a great clinician and described in great detail the clinical characteristics of ocular cancer.

Conclusion

Karl Stellwag von Carion followed the medical progress of his time and in the theme of ocular cancer he was influenced by Albrecht von Graefe (1828-1870) (Hirschberg, 1906), Rudolf Ludwig Carl Virchow (Virchow, 1863) and Hermann Jacob Knapp (1832-1911) (Knapp 1868). But although he accepted their pioneer studies in the field of ocular cancer he did not imitate them or uncritically accept their views. He used their studies and case reports on ocular cancer, which he verified and enriched with his patients and the pathology studies of his own cases. He was a reputable professor of ophthalmology and his medical studies, especially those concerning ocular cancer, were innovative marking the pathway in medical analysis of the disease. In addition, his textbooks were very important treatises with worldwide acceptance, because in a very methodic, simple but accurate way they taught his students and all ophthalmologists the modern medical thought concerning ocular cancer and ocular diseases in general, the recent achievements on these disease and how physicians could deal with the problem of differential diagnosis in their daily work. Stellwag's studies were a reference point for the world medical community of the time, his text book on practical ophthalmology was very helpful for every physician, while his atlas of ocular pathology was the first in history following the modern principles of medicine, which constituted a prototype of similar studies in the future.

Declaration

All authors declare no conflict of interest.

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