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Case Presentation

Brain Tumors Presumed Malignant without Biopsy-Evaluation and Treatment Problems

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Abstract

Patients with brain tumors may have the following issues: tumors are in deep or vital regions; they refuse the biopsy; the neurosurgeon does not reach the tumoral tissue and the biopsy is irrelevant; advanced cases, considered "outside the surgical and oncological therapeutic resources". These patients cannot receive oncological treatment or radiotherapy because of the restrictive indications of the insurers (health insurance companies) or because of the risk of allegations of malpractice. Patients will not receive some social security rights (short term sick leave, disability pension) in the same way as cancer patients, but only as a patient with a common illness. Patients can receive palliative treatment, can be hospitalized in oncology departments. We propose to discuss a separate diagnostic and treatment protocol for this group of patients, based on laboratory (ctDNA) and imagistic criteria. Assistive technologies using Computer Vision Model combined with Convolutional Neural Network may help classificate and diagnose these tumors.

Keywords: Brain tumor; Biopsy; Insurance medicine; Malpractice; Computer vision

Introduction

Cancer is a large group of diseases that can start in almost any organ or tissue of the body when abnormal cells grow uncontrollably, go beyond their usual boundaries to invade adjoining parts of the body and/or spread to other organs [1]. For the last 100 years, cancer was defined only based on histogenesis - cells of origine or similar microscopic features. In the classification of brain tumors, immunohistochemical characteristics were later added, and after 2016, also molecular parameters [2].

Brain tumors are divided into benign, more recently called "non-malignant" and malignant [1], primary and metastatic.

World Health Organization (WHO) Description of brain tumor grades [3]:

Grade I: These are the least malignant tumors and are usually associated with long-term survival. They grow slowly and look almost normal when viewed under a microscope.

Grade II: These tumors grow slowly and appear slightly abnormal under a microscope. Some may spread to nearby normal tissue.

Grade III: These tumors are malignant, although there is not always a significant difference between grade II and grade III tumors. The cells of a grade III tumor are actively reproducing, they are abnormal cells, which grow in the nearby normal brain tissue.

Grade IV: The most malignant tumorsreproduce rapidly, invading nearby normal brain tissue. These tumors form new blood vessels so that they can maintain their rapid growth. They may have an area of necrosis in the center [3,4].

Brain tumors are considered rare diseases, taken each type separately, although there are over 120 different types of primary brain tumors [1].

Nearly one-third (29.7%) of brain and Central Nervous System (CNS) tumors are malignant [1,4,5].

In the USA between 2013-2017, brain tumors were the most common form of cancer among children aged 0-14 years, as well as the leading cause of cancer-related deaths in this age group [5].

In the age group 15 and 39, for the period 2013-2017, malignant brain tumors were the third most common cancer [5].

In people over the age of 40, between 2013 and 2017, brain tumors were the 8th most common cancer and the third leading cause of cancer death [5].

As with any rare disease, according to EURORDIS, the correct diagnosis can take between 5 and 30 years [6,7]. Brain tumors have as their first symptom a headache, a quite common polymorphic symptom. This does not help to quickly diagnose this type of condition [5-7].

Sometimes the patient suffers a minor craniocerebral trauma, performs a brain CT or MRI, on which occasion asymptomatic brain tumors are highlighted. Sometimes you discover the cancer only at the autopsy, as reveils a study from Japan, where up to 24% of sudden unexpected cancer deaths have a definite diagnosis only post-mortem [8]

This poses particular problems in cases of brain neoplasms, because early detection and early treatment increase the life expectancy of these patients.

Therefore, many brain and CNS neoplasms are diagnosed in late stages, clinically and imaging, and the biopsy is no longer performed.

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Obtaining Treatment Based on Health Insurance-Problems in Practice

Any patient with normal tissue biopsy, although on imaging may have multiple space-occupying formations, with a clear malignant appearance, invasive, can not be classified as a cancer patient and does not benefit from specific treatment. Some oncologists resolve the uncertainty based on clinical and imagistic criteria, in support of the patient's access to treatment [9,10].

Any patient with a biopsy, diagnosed with borderline tumor, grade 2-3 (borderline 2), cannot receive cancer treatment because he does not meet the criteria for malignancy.

All patients in whom biopsy is not possible (deep layer tumor, high risk of bleeding, multiple tumors, life expectancy below 3 months [11]) have virtually no definite cancer diagnosis and cannot receive specific treatment.

These patients cannot receive oncological treatment or radiotherapy because of the restrictive indications of the insurers (health insurance companies) or because of the risk of allegations of malpractice. Patients will not receive some social security rights (short term sick leave, disability pension) in the same way as cancer patients, but only as a patient with a common illness [12]. Patients can receive palliative treatment, can be hospitalized in oncology departments.

Presentation of Clinical Cases

Case 1: A 57-year-old male doctor fainted in hospital following surgery for a hernia and suffered a minor brain trauma (2019). A brain MRI was performed urgently, which did not detect hematomas or other acute lesions, but highlighted: lesion in the right hippocampus, 3/2cm, which makes common body with the choroid plexus of the right lateral ventricle and develops in the right parietal white matter, formation in the left lateral ventricle 1cm, lesion in the anterior horn of the right lateral ventricle of 0.8cm, multiple lesions "in oil stain" with contrast substance lining the ventricles (including proximal 1/3 of the brainstem), a meningeal lesion in the upper portion of the cerebellar vernix.

After 2 weeks, he underwent a neurosurgical intervention for diagnostic purposes, with a superficial tumor biopsy, a biopsy limited by a bleeding of multiple neovessels. The biopsy indicated normal brain tissue.

Blood tests were normal, with no signs of inflammation (ESR 2mm/h, fibrinogen 317 mg/dl), only with 19% eosinophilia. The patient had no other diseases. The differential diagnosis was made with CNS tuberculosis [13,14], parasitosis, because the MRI result was extremely polymorphic. The patient was asymptomatic for another 2 months after the biopsy, then complaining of altered general condition, memory disorders, slowness in speech, loss of appetite. After 3 months from the diagnosis, another MRI and a cerebral angio-MRI were performed, observing the tumor growth by about 30% on each lesion. The opinions of the imaging doctors consulted ranged from a choroid plexus papilloma or a malignant tumor, including a glioblastoma.

Because of the defensive medicine, no biopsy result, polimorphic lesions, the pacient was refused by several oncologists and received only palliative treatment.

Motor disorders with unsafe gait appeared 10 months after diagnosis, requiring hospitalization. The patient died in a palliative care ward 11 months after the revealing accident.

The patient could not obtain medical leave for 548 days with 100% payment, as for oncological diseases, but only 183 days with 80% of the salary, as for a common illness (in Romania). He obtained a disability pension 6 months after the onset of the disease, based upon neurological signs and imaging, the diagnosis beeing "Multiple brain tumors".

Case 2: A 27-year-old male patient, operated for a borderline astrocytoma (glioblastoma), classified as a grade 2 tumor after the biopsy, presented to the insurance medicine office for retirement. This patient also did not benefit from medical leave for oncological disease and was retired based on neurological signs. The diagnostic for invalidity pension was „Borderline brain tumor, operated". The patient's evolution was undulating, with recurrences. The patient obtained oncological treatment after insistence, because there is no practical difference between grade 2 and grade 3 tumors, as state in an article published in 2015 and the WHO Description of brain tumor grades [3,4,15,16].

Case 3: A 45-year-old male patient with a tumor located near the base of the skull, in an area inaccessible for biopsy, inoperable, invasive, discovered late, presented for disability retirement. He was considered to have virtually no diagnosis. He did not receive oncological treatment. He was retired based on neurological syndromes, the diagnosis beeing "Inoperable brain tumor". The evolution was quickly unfavorable.

Discussions

The cancer model based solely upon histological findings is obsolete, especially for patients with brain tumors. The non-biopsiable patients can be diagnosed by other means, as cell-free circulating tumor DNA, used in non-small cell lung cancer and other malignant conditions [17].

Piccionni and all found ctDNA in 50% of meningiomas and glioblastomas, in a study in 419 patients, published in 2019 [18].

Non-biopsiable patients and their doctors may receive another help from AI, artificial intelligence.

Computer-assisted Physician Documentation/computer-aided medical diagnostic (CAD) were developped as early as 1950. In 1998, the first commercial CAD system for mammography, the Image Checker system, was approved by the US Food and Drug Administration (FDA). In the following years several commercial CAD systems for analyzing mammography, breast MRI, medical imagining of lungs, colon, and heart also received FDA approvals. Currently, CAD systems are used as a diagnostic aid to provide physicians for better medical decision-making [19,20].

Big progres was realised from 2015 till now in Computer Vision and Machine Learning, part of Artificial Intelligence. Imagenet project from 2009 gathered big data [21]. Because of the scientific collaboration in its realization, all this data is oppenly available for scientists. A lot of Neural Network applications were developped.

Convolutional Neural Network is one such application used for object recognition model. Steps for predictive modelling were huge. Now scientists use deep learning models in the cloud.

YOLO (You Only Look Once) system is an open - source method of object detection that can identify objects in images and video. In the last years the program got from 20 seconds per image to 20 miliseconds per image, so 1000 times faster, allowing very interesting medical applications, as real time image analyse in endoscopy, ophthalmology [22,23]. This computer assisted image analyse was better and more accurate than the human one, allowing small lesions detection [22].

Wang and Wu 2010 Results in Pathological Brain Detection (PBD), analysed over 160 images. They showed that the classification accuracy was 98.75% [24].

In 2014, Padma et al. used combined wavelet statistical texture features to segment and classify AD benign and malignant tumor slices [25].

Such progres may help develop a new diagnosis protocol for such non-biopsiable cases of brain tumors. This might reduce the time interval from the symptoms appearance to the diagnostic, as biopsy is usually hard to obtain and time consuming.

Should we rely only on computer tumor recognition? Probably not. But computers will perform in the future a more accurate and thorough exam of the brain CT, SPECT, PET or MRI imaging as a human, due to longer exam time, small detail detection, complete exam, and not least, due to huge databases embedded.

Conclusions

Brain tumors are extremely polymorphic and therefore are considered rare diseases (each type affects less than 1 person in 2000). Brain tumors are the most common cause of cancer death in children and adults under the age of 40 (in USA), and therefore must be more actively diagnosed.

The lack of a biopsy should not prevent the patient in obtaining cancer treatment, nor in obtaining social security rights.

I propose to neurologists and oncologists to develop a diagnostic and treatment protocol, based on imaging aspects for these non-biopsiable cases, which will still offer a chance at specific oncological treatment, with increased life expectancy. Computer Vision, Neural Networks and Deep Learning Models may offer in 2 years time diagnostic tools to differentiate non-malignant from malignant tumors of the central nervous system, for the non-biopsy cases.

It is not normal that in the 21st century we cannot overcome these barriers. It is not normal to leave patients untreated, and we are not just referring to neurosurgical treatment, which may sometimes not be indicated.

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