Long-time survival of a patient with glioblastoma and Turcot’s syndrome

Case report

HANS PETER RUTZ, M.D., NICOLAS DE TRIBOLET, M.D., JEAN MARIE CALMES, M.D., AND GERMAIN CHAPUIS, M.D.

Departments of Radiotherapy, Neurosurgery, and Surgery, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

A rare case of Turcot’s syndrome is reported in a long-time survivor of glioblastoma multiforme. The patient was treated for his tumor in 1976 with macroscopically complete surgical resection and radiotherapy consisting of 60 Gy to the tumor bed and 40 Gy to the whole brain. Five years later, in 1981, he developed adenocarcinoma of the colon Dukes Stage B which was successfully treated at another hospital by surgery alone. In 1990, he presented with multiple colon polyps and adenocarcinoma Dukes Stage A. For more than 15 years, the patient has been afflicted with cystic and conglobate acne. Possible mechanisms and treatment with 13-cis retinoic acid are discussed.

Key Words • Turcot’s syndrome • glioblastoma • colon cancer • familial polyposis coli • retinoic acid

LONG survival of patients with histopathologically documented glioblastoma is extremely rare. We present the case of a patient who, 14 years before his present admission, was treated for glioblastoma multiforme by neurosurgery and radiotherapy. He is still free of this malignant disease; however, he is currently suffering from his second primary adenocarcinoma of the colon.

Case Report

This 35-year-old man underwent neurosurgery and radiotherapy for a malignant glioblastoma multiforme in 1976, at 21 years of age. (This patient has previously been reported as Case 4 by de Tribolet, et al.) At that time he had suffered from severe cystic and sebaceous acne for several years. The histological appearance typical of glioblastoma was characterized by palisading of tumor cells around an area of necrosis. Remarkably, his older sister (Case 3) had died in 1968, at 15 years of age, of an inoperable brain tumor, but no histology was determined and no autopsy was allowed. From the present patient’s operative specimen, a tissue culture of the glioblastoma cells was established, and the malignant cells grew for 6 months. These cells had thus lost the mechanisms for contact inhibition, but were not immortalized.

Five years later, in 1981, the patient underwent surgery at another hospital for a well-differentiated adenocarcinoma of the colon, Dukes Stage B, T3N0M0. The last 9 cm of the ileum and the first 19 cm of the colon, including the appendix, were removed. At the patient’s request, two sebaceous cysts at the left side of the scrotum were excised; however, colonoscopy was not performed. The occurrence of this second cancer in the context of his sister’s brain tumor was not analyzed as a syndrome.

Nine years later, in June, 1990, the patient was hospitalized again. He presented with several polyps of the colon and severe treatment-resistant furunculosis (no retinoids had been applied). Therefore, the rest of the colon, except for the last 6 cm of the rectum, was removed. A large polyp (3 cm in diameter) located 15 cm from the anal margin was described histopathologically as an adenocarcinoma Dukes Stage A. In view of this association of glioblastoma and colon polyposis and cancers, his treatment-resistant cystic and conglobate acne, and his sister’s death from brain tumor, the patient was diagnosed as having Turcot’s syndrome.
Discussion

A disorder involving multiple sebaceous cysts associated with polyposis and adenocarcinoma of the colon is known as the Oldfield syndrome. This syndrome was subsequently extended by Gardner, who described the apparently dominant inheritance for intestinal polypos, sebaceous cysts, osteomas, and fibromas. Crail and Turcot, et al., on the other hand, described the association of familial polyposis of the colon with malignant tumors of the central nervous system, since known as Turcot's syndrome. This syndrome is characterized by the association of polyposis coli (which often leads to colon cancer) and primary neuroepithelial tumors of the central nervous system, particularly glioblastoma. The syndrome is sometimes accompanied by severe sebaceous cysts. Other forms of cancer may also occur, such as papillary carcinoma of the thyroid or acute myelomonocytic leukemia. To date, more than 50 cases have been reported in the literature, but in only 34 of these cases have both cerebral tumor and colonic polyposis been confirmed by histopathology.

Our patient thus can be classed as the 35th individual documented to be afflicted with Turcot's syndrome. This cluster of cancers occurring in a single person may be caused by a number of different possibilities. These include: a hereditary or nonhereditary form of a genetic disease involving a growth suppressor or deoxyribonucleic acid (DNA) repair gene; viral infection; carcinogen exposure; hereditary or nonhereditary immune deficiency syndrome; the random occurrence of multiple primary tumors due to bad luck; or a cause that escapes current scientific consideration. For patient management, identification of relatives and individuals in the general population at risk, as well as for genetic counseling, it is obviously important to better understand the nature of the syndrome.

All of these syndromes involving polyposis coli appear to be closely related to, if not a consequence of, genetic changes associated with polyposis coli, probably as a result of a mutation in the gene for familial polyposis on chromosome 5. In the case of larger deletions, they may involve neighboring genes and result in an association with a varying array of other symptoms. Remarkably, the first colon cancer in this patient was located in the ascending colon, the part where two-thirds of hereditary colon cancers without multiple polyps occur. His second colon cancer, which was associated with polyposis, was located in the rectum, the part where two-thirds of hereditary colon cancers with multiple polyps occur, along with the nonhereditary colon cancers. These findings strongly suggest the existence of genetic factors predisposing to cancer in this patient. His karyotype, however, showed no abnormality when analyzed with standard banding techniques, nor were there genetic markers for this syndrome. Therefore, it is currently not possible to diagnose his two children, 6 and 8 years of age. As it is likely that they are both at a 50% risk of being affected with the putatively hereditary cancer syndrome, they will be closely followed in the future with regular brain scans and sigmoidoscopy.

Another intriguing question concerns the apparently effective control of the glioblastoma in our patient by neurosurgery and radiotherapy. This is extremely rare. Astrocytomas grade III and IV are considered incurable despite any treatment attempt. However, six of 1147 patients survived for more than 10 years in a Swedish patient cohort, with youth being the only common denominator: no survivor was older than 38 years at operation. In addition, three of these six survivors were also treated with postoperative radiotherapy of up to 58 Gy. Macroscopically total resection along with both young age (21 years) and postoperative radiotherapy of 60 Gy to the tumor volume and 40 Gy to the whole brain are thus three favorable factors that may have allowed the long-term survival of this patient.

Several cellular and molecular mechanisms may normally underlie the deleterious malignancy of glioblastoma multiforme. The highly infiltrative nature, facilitated by membrane-bound metalloproteases, reduces the chance of complete resection to near zero. Apparent radioresistance results in failure to inactivate remaining microscopic or macroscopic disease by postoperative radiotherapy with doses tolerated by the brain. In the laboratory, it has been shown that glioblastoma cell lines are very radioresistant and repair-proficient when irradiated in vitro, particularly at low pH, caused by tumor glycolysis and hypoxia. On the other hand, it has been shown that fibroblasts from a patient with Turcot's syndrome were unusually sensitive to DNA alkylating agents and radiation. The same has also been observed for skin fibroblasts from a family with Gardner's syndrome. Although the clinical implications of this in vitro hypersensitivity to the lethal effects of radiation are currently unknown, it is possible that the increased sensitivity of the fibroblasts may be associated with heterozygosity of a gene underlying the disease, and that the tumor cells, presumed to be homozygous for the defective gene, might be even more sensitive than the normal cells. This hypothesis, however, awaits experimental testing. A defect in a molecular mechanism for the repair of DNA lesions in cells heterozygous for a functional growth suppressor gene associated with familial polyposis coli on chromosome 5 could obviously add an explanation for the high incidence of cancer in patients affected with this genotype. Such an association, for example, has previously been proposed for patients with an inactive allele of the retinoblastoma gene or certain other growth-suppressor or cancer-prone gene defects.

In view of the presumed increased risk of our patient to develop a fourth primary malignancy or a radiation-induced secondary cancer, and taking into account his therapy-resistant sebaceous cysts, we prescribed 1 mg/kg 13-cis retinoic acid per day, which will be adjusted to the patient's tolerance. Retinoids are well established for the treatment of resistant cystic and conglobate acne and their preventive effect on carcinogenesis.

H. P. Rutz, et al.
Glioblastoma and Turcot’s syndrome

A significant impact on the prevention of second primary malignant tumors in head and neck cancer has recently been demonstrated in a placebo-controlled, double-blind, randomized trial. Furthermore, some experiments indicate that certain retinoids may inhibit error-prone mechanisms for the repair of DNA damage, and retinoids are under consideration for the prevention of treatment-induced secondary cancer, based on their effects on the irradiated cells and on the well-documented stimulation of the immune system.

References


Manuscript received July 31, 1990.
Address reprint requests to: Nicolas de Tribolet, M.D., Service de Neurochirurgie, 1011 Lausanne-CHUV, Switzerland.