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Panniculitis Under Successful Targeted Inhibition of the MAPK/ERK Signaling Pathway in a Patient With BRAF V600E-mutated Spindle Cell Oncocytoma of the Pituitary Gland

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Abstract. *Background: Spindle cell oncocytoma (SCO) is a rare non-neuroendocrine neoplasm of the pituitary gland. In general, surgical excision and radiation therapy is performed. However, local recurrences are frequently seen, requiring repeated surgical and radio-oncological interventions. Thus, mutational analysis of the tumor and targeted therapy may represent a valuable therapy option in these patients. Case Report: A 38-year-old female patient with past medical history of 6 surgeries (two transsphenoidal and four transcranial), radiation therapy, and chemoradiation therapy due to several recurrences of a SCO, presented for follow-up imaging. MRI of the brain showed growth of a tumor in the right parasellar region consistent with a new local recurrence, which due to its size and location was considered to be not resectable. Molecular analysis of a previously surgically removed tumor showed a BRAF V600E mutation and thus, combined targeted inhibition of the MAPK/ERK signaling pathway using a BRAF inhibitor and a MEK inhibitor was started. Due to drug-induced panniculitis, MEK inhibitor had to be stopped and BRAF inhibitor only was continued, which was well tolerated by the patient. Subsequent imaging revealed tumor regression already four weeks after therapy initiation and no disease progression has been observed to date. Conclusion: A SCO patient with BRAF V600E mutation was successfully treated using targeted inhibition of the MAPK/ERK signaling pathway. Under therapy, tumor regression was observed and the patient has been free of progressive disease for more than two years now. Thus, mutational analysis and targeted inhibition may offer an effective treatment option for SCO patients, while potential side-effects to this therapy, like observed in our case, can occur and needs to be adequately treated.*

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Spindle cell oncocytoma (SCO) represents a rare non-neuroendocrine neoplasm of the pituitary gland (1, 2). After it was initially described by Roncaroli *et al.* in 2002 (1), it was included in the World Health Organization (WHO) classification of central nervous system (CNS) tumors in 2007 (3). Therapeutically, surgical excision as well as radiation therapy has been performed in these patients (2, 4, 5). However, local recurrences are frequently seen, which represent a major challenge as treatment options remain limited, to date (2).

Approved by the U.S. Food and Drug Administration (FDA) in 2015, the combined use of BRAF inhibitors, *e.g.* dabrafenib and vemurafenib, and MEK inhibitors, *e.g.* trametinib and cobimetinib, targeting the MAPK/ERK signaling pathway has become the first-line treatment for patients with BRAF V600E mutated metastatic melanoma (6, 7). These highly effective drugs in metastatic melanoma could also be beneficial in patients suffering from other tumor entities with BRAF mutation, including SCO.

In this article, we report the successful treatment of a patient with a BRAF V600E-mutated SCO of the pituitary gland using targeted inhibition of the MAPK/ERK signaling pathway, indicating that this might be an effective treatment option for this rare CNS malignancy. To our knowledge, such a case has not been reported in the literature to date.

Case Report

A 38-year-old female patient with SCO presented for follow-up imaging. Her past medical history included a total of 6 surgical excisions (two transsphenoidal and four transcranial), radiation therapy and chemoradiation therapy with five doses of cisplatin due to local recurrences. The last surgical excision was performed one year prior to the current presentation.

The current MRI of the brain showed a mass growth in the right parasellar region (Figure 1A) consistent with a local recurrence, which due to its size and location was considered to be not resectable. Molecular analysis of a previously surgically removed tumor showed a BRAF V600E mutation and thus, targeted inhibition of the MAPK/ERK signaling pathway using the BRAF inhibitor dabrafenib 150 mg twice daily and the MEK inhibitor trametinib 2 mg once daily was started.

Approximately one month later the patient presented with a 4-day history of painful nodules accompanied by fever. On physical examination, tender, erythematous, and well-demarcated papules, plaques, and nodules were seen on patient's trunk and extremities, with approximately 0.5-2 cm in diameter each (Figure 2). Cervical lymph nodes were enlarged. Arthralgia, itching, fatigue, or other general symptoms were denied. Blood tests showed elevated white blood cell count and C-reactive protein level. Histopathology of a deep skin biopsy from the left upper arm showed a diffuse lymphocytic infiltrate as well as neutrophilic granulocytes in the subcutaneous tissue, consistent with a lobular panniculitis. Given the patients' history, as well as the clinical and histological findings, BRAF and MEK inhibitor induced panniculitis was diagnosed. Pancreatic panniculitis was ruled out by normal amylase and lipase levels in the serum test, and by sonography of the abdomen. The combined therapy with dabrafenib and trametinib was stopped and a systemic therapy with prednisone *p.o.* and local treatment with glucocorticosteroids was started. This resulted in a significant improvement of symptoms within a few days.

For follow-up of the SCO, imaging with MRI of the brain was performed and tumor regression was seen four weeks after therapy initiation, consistent with a response to targeted therapy (Figure 1B). Thus, antitumor therapy was re-initiated after it was interrupted for 2 weeks. Also, due to observed side effects, the combination therapy was altered to the BRAF inhibitor vemurafenib 960 mg twice daily and the MEK inhibitor cobimetinib 60 mg once daily. After 12 days of treatment the patient again started to develop painful nodules, which were successfully treated with p.o. prednisolone and local glucocorticosteroids. The MEK inhibitor cobimetinib was stopped and the BRAF inhibitor vemurafenib only was continued, which was well tolerated by the patient.

The patient has been on vemurafenib for more than two years now. Under therapy, the patients' mass has been stable and no evidence of progressive disease has been observed in the follow-up imaging to date.

Discussion

Only few cases have been reported on SCO to date (2). It is generally seen in the sella region of the pituitary gland and thus, patients often present with vision loss, headache, or hypopituitarism (2). It affects female and male adults of middle to older age (2). As it is not possible to distinguish SCO from other pituitary tumors by imaging only, pathological assessment of the excised tumor is required for the diagnosis (2).

Histologically, SCO shows a fascicular pattern of spindle cells with eosinophilic cytoplasm (1, 8). While nuclear atypia is generally minimal and mitotic indices are low, expression of S-100, vimentin, galectin-3, and epithelial membrane antigen (EMA) is typical for SCO (1, 8). However, the lack of synaptophysin, chromogranin, and pituitary hormone expression, distinguishes a SCO from pituitary adenoma (1, 8). In addition, SCO in general does not express glial fibrillary acidic protein (GFAP), which is typically seen in pituicytomas (1, 8, 9).

Mutations in the MAPK/ERK signaling pathway (also known as the Ras-Raf-MEK-ERK signaling pathway) play a major role in the development of different tumor entities, as defects in this pathway may lead to an uncontrolled tumor growth (10). Thus, therapeutic agents targeting different compounds of this signaling pathway can lead to tumor regression (6, 7). BRAF inhibitors as well as MEK inhibitors, which both block different steps of the MAPK/ERK pathway, are successfully used in *e.g.* metastatic melanoma patients with BRAF V600E mutation (6, 7). BRAF mutation has also been reported in cases of non-small cell lung cancer (11), glioblastoma (12), or Langerhans cell histiocytosis (13).

In our patient, BRAF V600E mutation was detected in the molecular analysis of the tumor and combined treatment by BRAF and MEK inhibitor fortunately resulted in therapeutic response with tumor regression within 4 weeks. Although the treatment had to be interrupted due to side effects when combination therapy was given, BRAF inhibitor therapy alone has been continued, which is well tolerated by the patient and has led to a stable disease for over two years. Especially in our patient, who had to undergo repeated surgical interventions as well as radiation and chemoradiation therapy due to repeated local tumor recurrences, this successful treatment is very encouraging and promising.

In 2016 Miller *et al.* already reported four patients with SCO, where abnormal MAPK/ERK pathway signaling was observed in whole exome sequencing of the tumor, suggesting

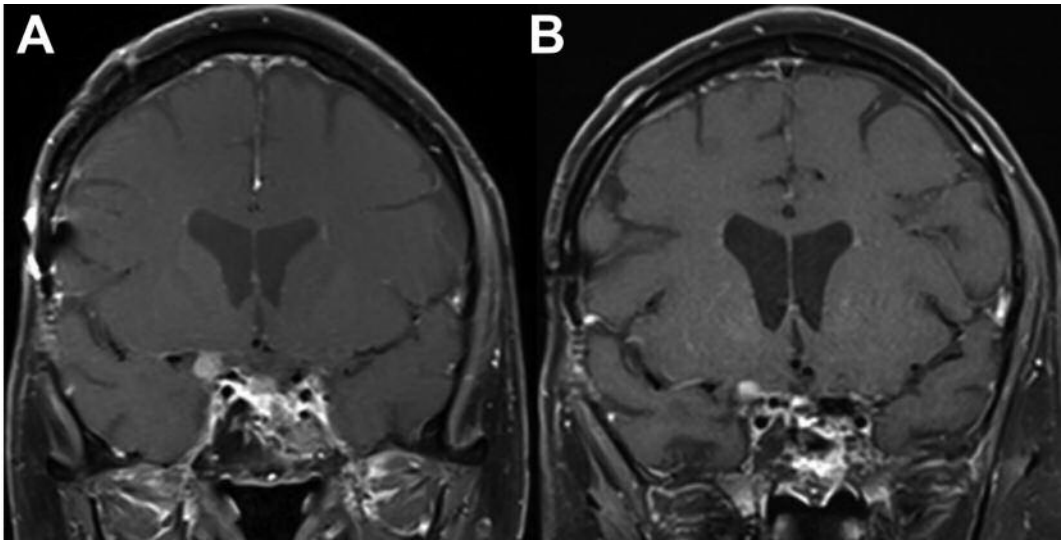

Figure 1. *MRI of the brain showing the tumor in the right parasellar region of the pituitary gland (A) prior to targeted therapy initiation, as well as (B) four weeks after therapy initiation with recognizable tumor regression*.

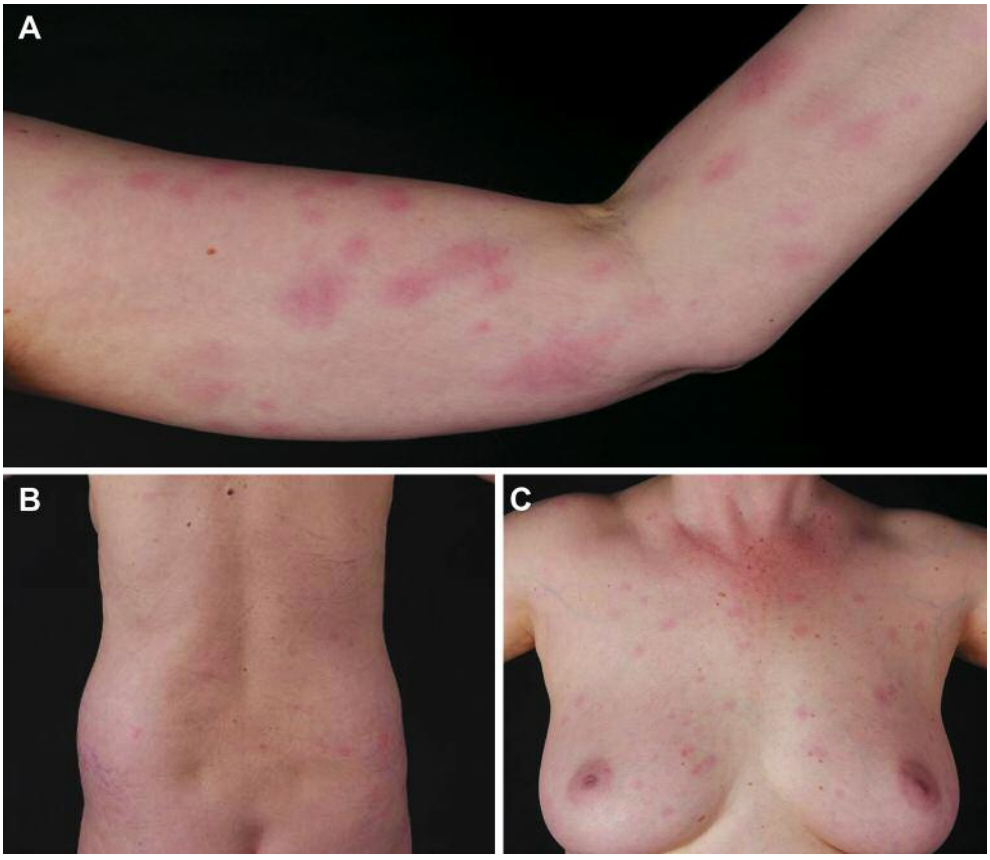

Figure 2. *Clinical presentation of the patient approximately four weeks after initiation of targeted therapy with tender, erythematous, and well-demarcated papules, plaques, and nodules on (A) patients left arm and (B+C) patient's trunk*.

that targeted inhibition of the MAPK/ERK pathway may offer an effective treatment option for SCO patients, especially in non resectable tumors or patients with several recurrences (14). Our presented case supports these findings.

As targeted inhibition of the MAPK/ERK signaling pathway is an approved first-line therapy in *e.g.* metastatic melanoma patients with BRAF V600E mutation, potential side effects are well known (6, 7). Panniculitis has been reported as a rare adverse effect induced by BRAF inhibitors (15), MEK inhibitors (16) and the combined administration of both agents (17). In our patient, drug-induced panniculitis was observed, which typically affects predominantly upper and lower extremities (17). As our patient did not develop further lesions during BRAF inhibitor treatment only, MEK inhibitor was the suspected causing agent. The exact pathomechanism of this adverse effect is not yet fully understood and thus, further investigation is required.

Taken together, a SCO patient with BRAF V600E mutation was successfully treated using targeted inhibition of the MAPK/ERK signaling pathway. Under therapy, tumor regression was seen and the patient has been free of progressive disease for more than two years now. Potential side-effects to this therapy, however, can occur and needs to be adequately treated. Nevertheless, mutational analysis and targeted inhibition may offer an effective and promising treatment option for patients suffering from SCO.

Authors' Contributions

L.S.: Patient care, data collection, writing and revising the article; S.L.: Patient care, analysis and interpretation, revising the article; M.E.: Patient care, analysis and interpretation, revising the article; U.U.: Patient care, data collection, analysis and interpretation, writing and revising the article. All authors read and approved the final manuscript.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

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