9q22.3 Microdeletion Syndrome with Multiple Basal Cell Carcinomas Treated with Vismodegib: Three Key Messages in One Patient

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Gorlin syndrome (GS) is a well-described autosomal dominant cancer predisposition and multiple malformation syndrome. Most cases of GS are due to loss-of-function mutations in the *PTCH1* gene, which maps to chromosome 9q22.3 (1, 2). Large chromosomal deletions that involve *PTCH1*, identified by chromosomal microarray analysis, are the cause of 9q22.3 microdeletion syndrome. The phenotype of this contiguous gene deletion is separated from classic GS (3–6) by features such as metopic craniostenosis, obstructive hydrocephalus, macrosomia, important developmental delay and an increased risk of Wilms' tumour and leiomyoma (7).

The initial management of basal cell carcinoma (BCC) in patients with GS is surgical resection. Vismodegib is approved in France for the treatment of adults with metastatic BCC or localized BCC with recurrence following surgery or who are not candidates for surgery or radiation. The major adverse reactions are alopecia, muscle spasms, dysgeusia, fatigue, nausea, diarrhoea and arthralgia. The median duration of response to treatment is approximately 7.6 months (8).

We report here a case of a woman carrying a 9q21.33q22.3 microdeletion with phenotypic features typical of 9q22.3 microdeletion syndrome and multiple BCCs.

CASE REPORT

The patient was first seen in our department when she was 17 years old. She was the second of 2 sisters of healthy, non-consanguineous parents. At birth, she had dysmorphic features with macrocephalia, hypertelorism and a divergent strabismus, multiple calcifications of the falx cerebri and several skeletal abnormalities: kyphoscoliosis, syndactyly of the 3rd and 4th left toes, and an additional finger on the left hand. During childhood she had been surgically treated for multiple odontogenic keratocysts of the jaw, a left hydronephrosis and a left kidney cyst. She had no palmar pits and no cardiac or ovarian fibromas. She also had a metopic craniostenosis resulting in trigonocephaly complicated by an obstructive hydrocephaly requiring ventriculo-peritoneal shunting. Cerebral tomography revealed asymmetrical ventricles. She developed epileptic seizures when she was 11 years old and she had severe intellectual disability. At the age of 12 years, she began to develop multiple cutaneous tumours on the head corresponding to BCCs. Numerous surgeries were performed under general anaesthesia during childhood and hundreds of BCC were excised. The diagnosis of GS was made based on the presence of 3 major (BCC prior to 20 years of age, odontogenic keratocysts of the jaw, calcification of the falx cerebri) and 3 minor criteria (macrocephalia, skeletal malformations, and ocular abnormalities including strabismus) supporting this diagnosis (9). Sequencing of *PTCH1*, performed when she was 29 years old, did not detect a mutation. Seven years later, a comparative genomic hybridization microarray analysis (Agilent® 180K) revealed a 11.6 Mb interstitial 9q21.33q22.3 deletion (arr[hg19] 9q21.33q22.3(90,160,795-101,792,531) x1]). This deletion encompasses over 50 OMIM genes, including *PTCH1* and *FANCC*.

During follow-up, the patient developed more than 1,000 BCCs (a mean of more than 20 new BCCs per month), which were surgically removed. No other patient followed-up for GS at our institution developed nearly so many BCCs. At one time she had dozens of BCCs on the face and the plastic surgeon consultants were of the opinion that there were no further surgical possibilities. During this period, vismodegib became available in France and treatment was initiated. Fifteen days after the start of treatment, the patient developed a maculopapular eruption on her body and hands, with arthritis of the ankles (**Fig. 1**), without taking any other recently introduced drug. Complete blood count, liver tests and renal function were within normal range. As the medication was considered essential, and as there was no sign of severe drug reaction, such as Nikolsky sign, mucosal involvement or confluence of erythema, we decided to "treat through hypersensitivity" after consent of the patient's mother and under strict medical supervision while the patient was hospitalized. Within a few days, the eruption disappeared, although vismodegib was continued.

One month after the start of treatment there was a substantial response with regression of most of the BCCs. Within 6 months, all BCCs had regressed (**Fig. 2**). The patient developed alopecia and diarrhoea, but the latter could be controlled with symptomatic treatment.

To date, the patient has been treated for more than 3 years with vismodegib with a good tolerance and with no new BCCs. Furthermore, her mother has reported that some cognitive functions have improved under treatment. For example, she has begun to interact, speak, smile and help her mother in activities such as undressing.

DISCUSSION

This unusual case of GS bears 3 important messages: the importance of performing chromosomal microarray ana-

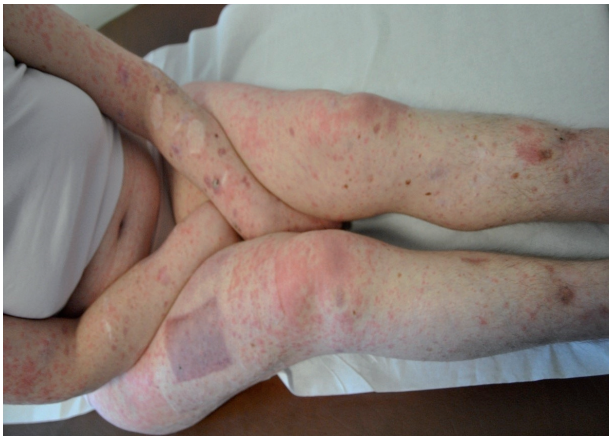

Fig. 1. Maculopapular eruption 15 days after the beginning of vismodegib.

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lysis in the absence of *PTCH1* mutation; the possibility of treating through hypersensitivity in case of vismodegib-induced maculo-papular drug eruption without signs of severity; and an unexpected, complete and durable response to vismodegib therapy.

The phenotypic spectrum associated with the 9q22.3 microdeletion is variable and depends on the size of the deletion. The minimal critical region includes the genes *PTCH1* and *FANCC*. Our patient carries a large deletion, which includes the entire coding sequence of *PTCH1* and *FANCC*, resulting in a severe phenotype with a very high incidence of BCCs compared with patients with a mutation affecting the *PTCH1* gene. Haploinsufficiency of *PTCH1* seems to account for most of the features described in 9q22.3 microdeletion, but is not sufficient to explain all the clinical phenotype. Most reported patients carry a deletion encompassing several genes, which might contribute to the additional features that are not expected in GS, such as *ASPN*, which is probably implicated in kyphoscoliosis observed in the case report (4, 10).

Drug rash with vismodegib has only rarely been reported (11), including a case of drug hypersensitivity without cutaneous eruption (12). In our case, vismodegib was continued despite the eruption. This is generally not recommended, but there was no other therapeutic option and there were a huge number of tumours with no surgical possibilities. The eruption resolved spontaneously, despite continuation of vismodegib. This has been reported under the designation "treating through hypersensitivity" in patients with human immunodeficiency virus (HIV) (13).

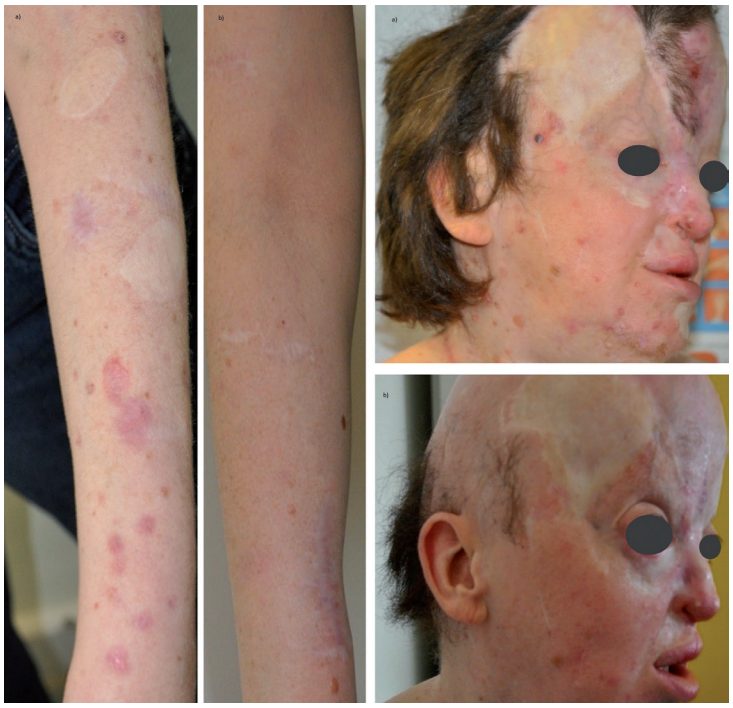

Fig. 2. (a) Numerous basal cell carcinomas (BCCs) on the face and forearm (note, also multiples scars on the face, due to previous surgeries). (b) Response to vismodegib with resolution of BCC on the face and arm after 6 months. Permission is given to publish these photos.

Intermittent treatment was attempted in order to limit side-effects in this patient, but each time we tried to treat on alternate months a few lesions recurred. Furthermore, treatment is overall well tolerated, so we decided to maintain continuous treatment.

Finally, the durable efficacy of vismodegib is notable in this patient. After 6 months of treatment, all the tumours had regressed. The duration of response to date is more than 3 years (11, 14).

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