

Rhinitis and epistaxis in patients treated by anti-angiogenic therapy

V. Prulière-Escabasse · E. Escudier · R. Balheda ·
J. C. Soria · A. Coste · C. Massard

Received: 11 June 2008 / Accepted: 29 July 2008
© Springer Science + Business Media, LLC 2008

Summary Anti-angiogenic therapies have a particular drug-related toxicity profile including hypertension, thrombosis, haemorrhages, and proteinuria. Moreover, patients treated by angiogenesis inhibitors present nasal symptoms including symptomatic rhinitis and epistaxis. For the first time, a new entity of “atrophic rhinitis” induced by angiogenesis inhibitors is described and revealed that angiogenesis inhibitors alter the differentiation of nasal epithelium. VEGF may act on epithelial cell proliferation and differentiation in nasal epithelium.

Keywords Angiogenic therapy · Rhinitis · Epistaxis · VEGF

The development of angiogenesis inhibition as a cancer treatment is a revolution in the paradigm of strategies against cancer [1]. Targeting of vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptors (VEGFRs) has lead to substantial clinical benefits in variety of solid tumors including renal cell carcinoma,

breast cancer, lung cancer and colon cancer, with three molecules currently registered: bevacizumab, sunitinib and sorafenib [2]. This new class of agents (anti-angiogenic compounds) encompasses a new drug-related toxicity profile including hypertension, thrombosis, haemorrhages, and proteinuria, which could provide more insight into the physiology of angiogenesis in normal tissue.

Recently, some patients treated by angiogenesis inhibitors (bevacizumab, sorafenib and sunitinib) reported nasal symptoms including symptomatic rhinitis and epistaxis. There is no data on the physiopathology of this side effect. We took advantage of two ongoing phase I trials at our center to investigate the occurrence of epistaxis and rhinitis in three patients treated by VEGF-TRAP (aflibercept, a fusion protein blocking VEGF) in combination with chemotherapy, and two patients treated by a small molecule inhibitor of VEGFR2, HER1 and HER2.

We first evaluated seven nasal symptoms using a semi-quantitative score (0: absent; 1: mild; 2: moderate; 3: severe): nasal obstruction, rhinorrhea, facial pain, loss of sense of smell, epistaxis, crusts and purulent secretions. A global symptom score was calculated by adding the different symptoms score. The average global score of nasal symptoms was 7 ± 2.5 (on a maximal scale of 21). None of the patients complained of facial pain or purulent secretions and sense of smell was always conserved. Nasal obstruction and rhinorrhea were constant in all patients. Nasal obstruction was moderate or severe while rhinorrhea was moderate (for 3/5 patients). The main disabling complaint was epistaxis and crusts present in all patients. The frequency of epistaxis was mild or moderate (for 4/5 patients).

After local anesthesia, we then performed a nasal endoscopy to evaluate both nasal mucosa and secretions. In all patients, we observed ischemic areas characterized by

V. Prulière-Escabasse · A. Coste
Service d'ORL et de Chirurgie Cervico-Faciale,
Hôpitaux H. Mondor (Assistance Publique Hôpitaux de Paris)
et Centre Hospitalier Intercommunal de Créteil,
Paris, France

E. Escudier
Service de Génétique et Embryologie Médicales Hôpital
Armand Trousseau (Assistance Publique Hôpitaux de Paris)
et U654,
Paris, France

R. Balheda · J. C. Soria · C. Massard (✉)
Department of Medicine, Phase I Unit,
Institut Gustave Roussy,
Villejuif 94800, France
e-mail: christophe.massard@igr.fr

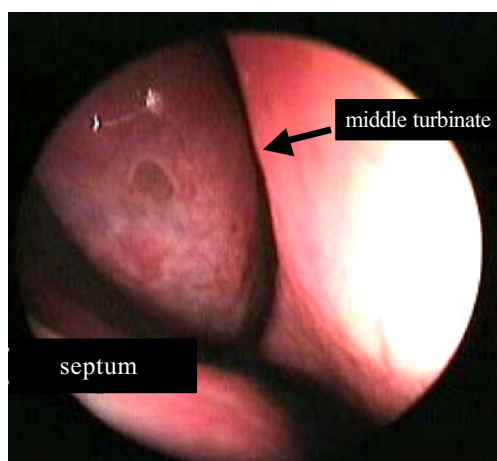


Fig. 1 Nasal endoscopy: pale blue color of the head of middle turbinate with a necrotic central lesion

a pale blue color of mucosa at the surface of septum and turbinates mucosa (especially at the level of middle turbinate). A faint oedema and ecchymosis were detected all along the surface of nasal mucosa, which was easily bleeding in contact with the endoscope. Small crusts were noted in all patients on turbinates and septum. (Fig. 1). During each endoscopy secretions were sampled with a suction tube for bacteriological analysis and mucosa of the posterior area of inferior turbinate was brushed for cytological analysis, as previously described [3]. All direct examinations were negative. In cultures, we found Gram positive Cocci in one case and *Corynebacterium* in two

cases. Nasal cytology was never normal (i.e. numerous ciliated cells, some basal and mucous cells). All the samples presented with blood contamination and inflammatory reaction composed of non-altered poly-morphonuclear neutrophils. The number of ciliated and mucous cells was low in three and four patients respectively, or absent in two and one patients respectively. Squamous cells, absent in normal nasal mucosa, were present and abundant in almost all the samples (Fig. 2).

This study demonstrates for the first time that new molecular angiogenesis inhibitors induce nasal symptoms with an unusual appearance of nasal mucosa. Nasal endoscopy and cytology revealed a loss of differentiation of epithelial cells and clear inflammation. Nasal symptoms and epithelial cell alterations were similar in patients treated with agents targeting either VEGF or VEGFR. In nasal mucosa, VEGF is normally detectable in human nasal epithelial cells [4] and overexpressed during viral rhinitis where it plays an important role in angiogenesis and capillary permeability. VEGF may also act on epithelial cell proliferation and differentiation as demonstrated in distal airways [5]. Thus, inhibition of VEGF expression in nasal epithelial cells could interfere with epithelium remodelling.

For the first time, our study describes a new entity of “atrophic rhinitis” induced by angiogenesis inhibitors and revealed that angiogenesis inhibitors alter the differentiation of nasal epithelium. However the long-term consequences of this phenomenon remain to be evaluated by a prospective study to better understand the pathophysiology of this side effect.

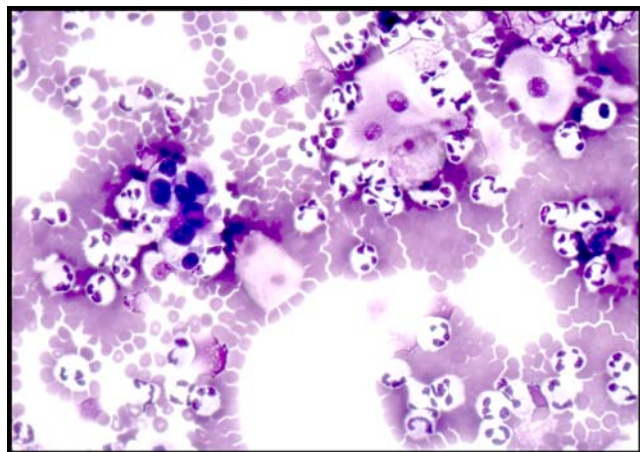


Fig. 2 Typical nasal cytology presenting loss of epithelial differentiation with blood contamination, numerous poly-morphonuclear leucocytes and squamous cells

References

1. Ferrara N, Kerbel RS (2005) Angiogenesis as a therapeutic target. *Nature* 438(7070):967–974 doi:10.1038/nature04483
2. Kerbel RS (2008) Tumor angiogenesis. *N Engl J Med* 358 (19):2039–2049 doi:10.1056/NEJMr0706596
3. Lalej-Bennis D, Boillot J, Bardin C, Zirinis P, Coste A, Escudier E et al (2001) Efficacy and tolerance of intranasal insulin administered during 4 months in severely hyperglycaemic type 2 diabetic patients with oral drug failure: a cross-over study. *Diabet Med* 18 (8):614–618 doi:10.1046/j.1464-5491.2001.00528.x
4. Coste A, Brugel L, Maître B, Boussat S, Papon JF, Wingerstmann L et al (2000) Inflammatory cells as well as epithelial cells in nasal polyps express vascular endothelial growth factor. *Eur Respir J* 15 (2):367–372 doi:10.1034/j.1399-3003.2000.15b24.x
5. Brown KRS, England KM, Goss KL, Snyder JM, Acarregui MJ (2001) VEGF induces airway epithelial cell differentiation in human fetal lung in vitro. *Am J Physiol Lung Cell Mol Physiol* 281:1001–1010