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Case report

Interventional bronchoscopy for HPV 16 and 66 with the use of spraying interferon-α (2b) plus bevacizumab and anti-reflux agent

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ABSTRACT

A fifty year old male was diagnosed with bronchial HPV. He was treated with local interventional treatment argon plasma coagulation and subcutaneous injections bevacizumab. Spraying of the regions followed with a specially designed catheter with interferon-α (2b). Systematic treatment of esomeprazole was also administered. After six months the patient is disease free and on close follow-up.

1. Introduction

Human papilloma virus (HPV) can diagnosed in the bronchial tree and there are several cases reported [1–3]. Depending on the virus strain there are cases of malignant transformation and benign atypia [1,2,4–6]. In the case of bulky disease interventional bronchoscopy is the solution for bulky endobronchial disease [7]. We can use mild sedation with fiber optic bronchoscopes or general anesthesia with rigid bronchoscopes [8]. Jet-ventilation is the optimal mode of ventilation [7,9]. We can argon plasma coagulation, YAG laser, basket and forceps with coagulation simultaneous application [10]. Based on the findings we can perform only local therapy with or without additional systematic therapy [11,12]. We can use celecoxib [13], Anti-reflux drugs [14], HPV vaccine [15], MUMP's Vaccine [16], Bevacizumab [17], indole-3-carbinol [18], cidofovir [19] and heat shock protein [20] as adjuvant treatment to debulking. In our case we used argon plasma coagulation probe (APC), subcutaneous injections of bevacisumab and local interferon-α spraying through a special designed probe [21,22]. Moreover; anti-reflux agent was administered based on the newly published therapeutic studies [21,22].

2. Case

A fifty year old male was submitted for persistent cough with initiation prior to two months. The patient was a smoker and a computed tomography of the thorax without intravenous administration did not

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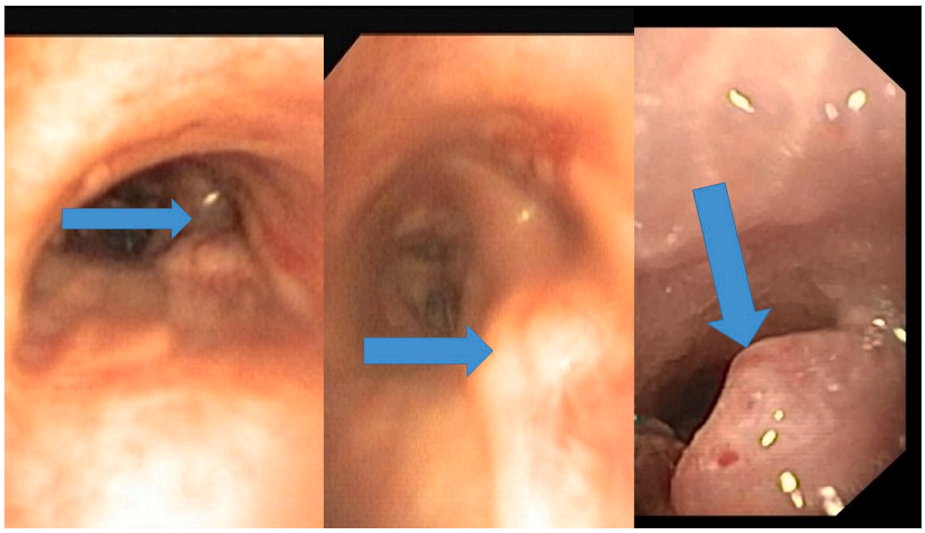

Fig. 1. Blue arrows indicate the different lesions within the respiratory airway. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

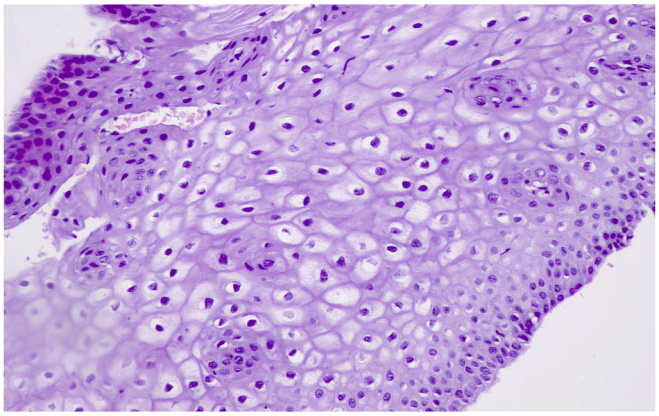

Fig. 2. Squamous bronchial epithelium with koilocytes (H&E X100). Real-time PCR revealed HPV infection positive in HPV high risk 16 & 59 subtypes).

reveal any pathology. A bronchoscopy was performed and biopsies from small localized lesions revealed HPV 16 and 66. (Figs. 1 and 2). Local treatment with argon plasma coagulation (APC) for larger lesions and local treatment with subcutaneous bevasizumab (7.5mg) injection followed (Fig. 3). In the region of the lesions we sprayed interferon-α (2b-recombinant) with a spraying catheter probe (Figs. 4–6). We administered anti-reflux therapy twice daily (esomeprazole 40mg) for the next six months, and with a new endoscopy no disease relapse was observed. We will perform another endoscopy after six months for re-evaluation.

3. Discussion

Interventional pulmonology is providing the solution for several cases where there is bulky disease. However; in order for a therapy to be effective we have to minimize disease relapse. Several treatments have been proposed such as anti-reflux drugs and vaccinations [22]. These drugs do not act immediately and they can be used as an adjuvant treatment to the primary treatment, they prolong the disease free time. In the case of extended tracheal disease, bevasizumab subcutaneous

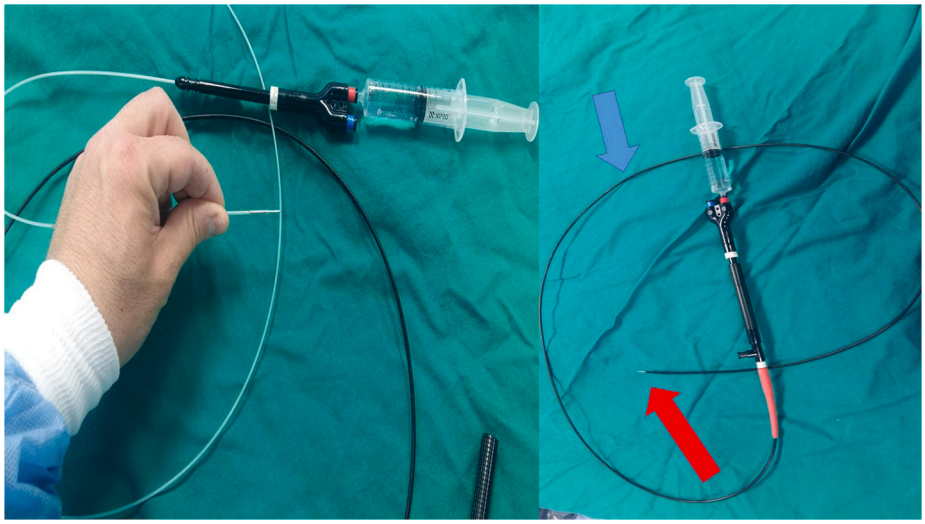

Fig. 3. Needle 19G for the subcutaneous injection of bevasizumab. Left the drug connected to the needle inlet, without the protective sheath. Right, the 19G needle (RED arrow) inside the protective sheath (BLUE arrow) as it is inserted in the bronchoscope. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

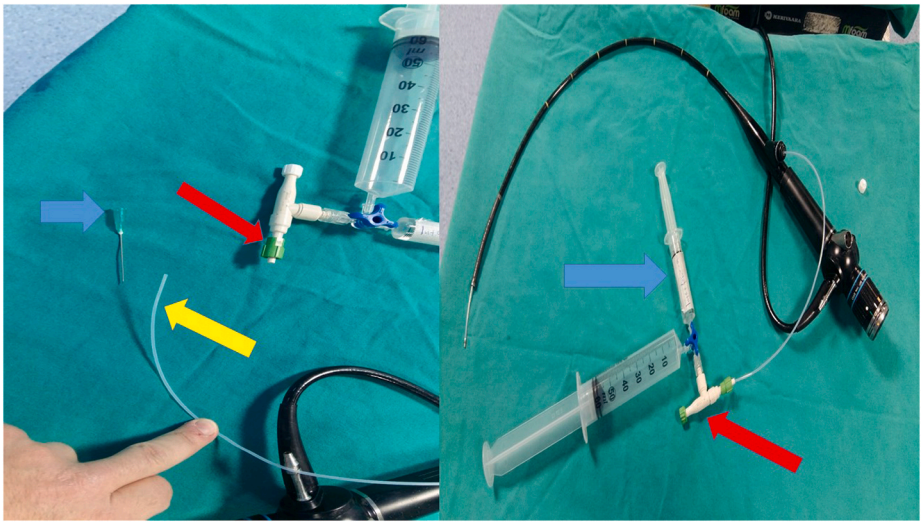

Fig. 4. Left; the blue arrow indicates the needle which is inserted in the spraying catheter (yellow arrow). The needle is connected to the inlet of the catheter red arrow. Right; Blue arrow indicates the drug (interferon-α), the spraying catheter is inside the bronchoscope and the green tip represent the stylet which is inside the catheter in order to make the catheter for stable when inserted in the bronchoscope. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

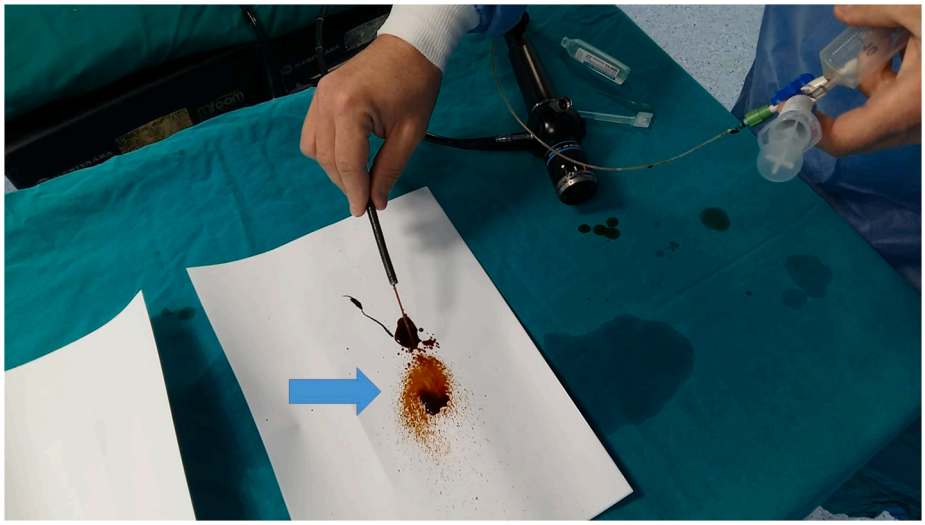

Fig. 5. We have added in the specific figure iodine solution in order to present the spraying ability of the catheter (BLUE arrow). We used a large needle of 60 cc in order to push and produce air compression. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

injections along with interventional pulmonology and systematic administration is an option [21,22]. Moreover; other drugs such as; celecoxib, indole-3-carbinol and cidofovir have been used with less efficiency than interferon-α [22]. The HPV virus definitely responses to immunotherapy and we should find ways to apply these drugs locally to the trachea [23]. In the current case we used local and systematic treatment, since usually we have disease relapse in the surrounding tissue after the first treatment. There is inoculation which cannot be observed as it is in a microscopical level and therefore spraying the region with immunotherapy can prevent disease relapse. Human papillomatovirus virions target aspects of the innate immune system. Normal keratinocytes express low levels of interferons in the absence of viral infection. HPV infection modulate the response to interferon. The major effect is that the levels of interferon-inducible genes are reduced in HPV-infected cells from that seen in normal keratinocytes. The addition of interferon still induces expression of these interferon-inducible genes but at initially reduced rates. Following 24 h of exposure to interferon, the levels of expression, increases to that seen in normal cells. Moreover; HPV proteins directly target components of the innate immune system to inhibit their action. Until recently interferon treatment has been used in treating patients with genital warts induced by low-risk HPV types but show mixed results in treating low-grade lesions and cancers induced by high-risk HPVs. HPV proteins have a number of strategies to overcome the effects of interferon. Treatment with interferon is more effective if combined with other therapeutic agents [24]. HPV viral oncogene products E6 and E7 have been shown to increase vascular endothelial growth factor (VEGF) via interactions with hypoxia inducible factor 1-alpha (HIF-1alpha). VEGF is known to play a significant role in the development of papilloma and may be a molecular target for the treatment of recurrent respiratory papilomas. Bevacizumab is a recombinant humanized monoclonal antibody that binds and inhibits VEGF by preventing receptor activation. It is not currently approved by the US Food and Drug Administration (FDA) for recurrent respiratory papilomas, however; preliminary studies have demonstrated the efficacy of bevacizumab in the treatment of localized upper airway RRP using both intralesional and systemic administration [17,21,25–28]. The usual side effects of bevacizumab treatment include renal failure, hypertension, bleeding, proteinuria, and bowel perforation [29]. New drugs for recurrent respiratory papilomas under investigation are tyrosine kinase inhibitors (TKIs) supported, by preclinical studies that have targeted

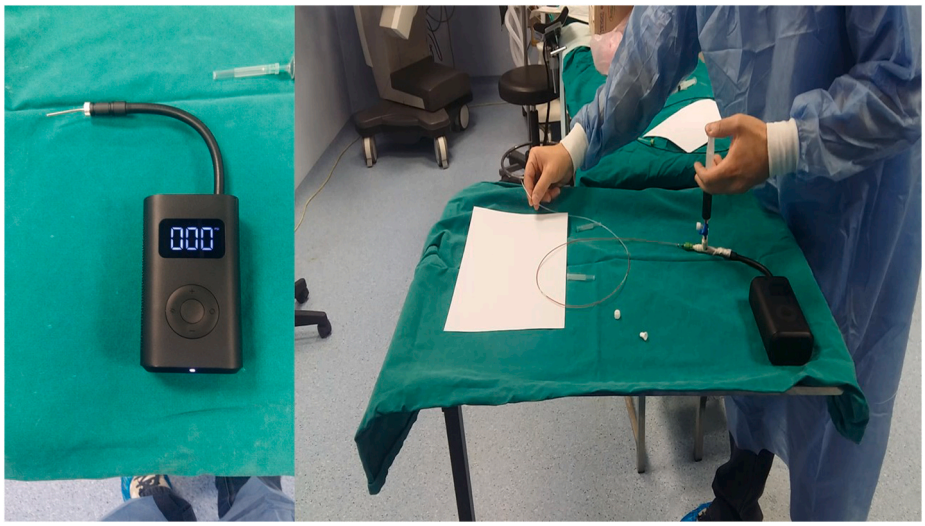

Fig. 6. Left; compression system, Right; after experimentation we used the presented compression system as it is connected on the right in order to enhance the spraying capability of the catheter.

epidermal growth factor receptor (EGFR) [30]. There also ongoing clinical trials with anti-PD1 (NCT02632344) and anti-PDL1 (NCT02859454) therapy for RRP. Close follow-up is necessary and definitely a case by case approach is needed for every patient. Our spraying system definitely added in the local disease control.

Declaration of competing interest

All authors declare no conflict of interest.

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