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BRIEF COMMUNICATION

Familial Clustering of Nasopharyngeal Carcinoma in Non-Endemic Area. Report of Three Families☆

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KEYWORDS
Nasopharyngeal carcinoma;
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Abstract Nasopharyngeal carcinoma is the predominant tumour type arising in the nasopharynx. Its aetiology is multifactorial; racial and geographical distribution, EBV infection and environmental exposure to specific substances are considered risk factors.

This condition is endemic in some Asian areas, where a genetic predisposition in its oncogenesis has been established. There is a strong susceptibility between nasopharyngeal carcinoma and HLA, where related specific haplotypes have been found.

In areas where the incidence is low, there are few reported cases of families affected. We report 3 cases of families with nasopharyngeal carcinoma among siblings, in the non-Asian population, probably related to EBV infection.

PALABRAS CLAVE
Carcinoma nasofaríngeo;
Etiología;
Agregación familiar;
Área de baja incidencia

Carcinoma nasofaríngeo familiar en zona no endémica. Presentación de 3 familias

Resumen El carcinoma nasofaríngeo es el tumor más frecuente que surge en la nasofaringe. Su etología es multifactorial, considerándose como factores de riesgo la distribución racial y geográfica, la infección por el virus de Epstein-Barr (VEB), así como la exposición ambiental a determinas sustancias.

Esta afección es endémica en algunas zonas asiáticas, donde se han encontrado predisposición genética en su oncogénesis. Existe una fuerte susceptibilidad entre el carcinoma de nasofaríngeo y el HLA, donde se han encontrado haplotipos relacionados específicos.

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En zonas donde la incidencia es baja, existen pocos casos publicados sobre familias afectadas. Reportamos 3 casos de familias con carcinoma de nasofaringe entre hermanos, en población no asiática, probablemente relacionada con la infección por el VEB.

Introduction

Nasopharyngeal carcinoma is a neoplasia of squamous cells that arises in the epithelium of the upper lining in the retropharyngeal cavity. There are some 86,000 new cases of nasopharyngeal carcinoma and 50,000 deaths a year from it.[1] Its aetiology is multifactorial and the following are considered to be factors of risk: racial and geographic distribution, infection by Epstein–Barr virus (EBV), and consumption of salted fish, fermented or room-temperature fats and other tinned foods that contain cancer-causing nitrosamines, as well as environmental and work exposure to formaldehyde or dust and wood-treatment preservatives.[2] It is slightly more common in males (2–3:1), and it usually appears at ages over 50 years.[3]

The incidence is rare in the United States and Western Europe, from about 0.5 to 2 cases per 100,000 inhabitants per year. In contrast, it is endemic in the south of Asia, and in the Esquimo population in Alaska and Greenland, where the incidence can reach 30 cases per 100,000 inhabitants per year.[3] Familial clustering has been widely observed in this population, with a frequency of around 10%. This suggests that inherited genetic predisposition is involved in its oncogenesis. The areas with intermediate risk include southeast Asia, northern Africa, Maghreb and the Middle East, and the Arctic, with an incidence of from 5 to 7 cases per 100,000 inhabitants.[4]

Familial clustering of nasopharyngeal carcinoma in areas of high incidence is well documented; genetic anomalies have been found in several genes, such as the one located in chromosome 3 (RASSF1A gene, related with DNA repair) and genotype c2/c2 of cytochrome P450 2E1 (X2,6 RR).[3] The involvement of genetic factors in its development is widely accepted and familial risk is among the group higher than any other malignant tumours in endemic areas.[5,6]

There are many genome-wide association studies in which a strong susceptibility of nasopharyngeal carcinoma is identified with the major histocompatibility complex in the region of chromosome 6p21 where the genes of human leucocyte antigen (HLA) are found, especially types A2, B14 (Asia), A10, B13, B18 (Maghreb) and B5 (in the Caucasian race).[7,8] However, 2 studies carried out in areas of high incidence (1 in the south of China and the other in Taiwan) have shown that the increase in the risk of nasopharyngeal cancer in these families is limited to non-genetic factors.[9,10]

In the areas of low incidence, the familial patterns of risk are not well documented. It is thought that various aetiological factors might be involved in the pathogenesis of different histopathological types of familial nasopharyngeal carcinoma.[11,12] Understanding the risk of cancer among the relatives of patients with nasopharyngeal carcinoma in areas of low incidence can lend us an idea of the possible genetic or environmental factors of risk shared between nasopharyngeal carcinoma and other malignant tumours.

Methods

A retrospective analysis was performed on the case histories of the patients with a diagnosis of nasopharyngeal carcinoma, during the period between 1993 and 2015, who presented history of relatives with the same diagnosis, seen at the Service of Medical Oncology in Salamanca (Spain). Six patients, from 3 Caucasian families, were identified. The patients were first-degree relatives (siblings) with a diagnosis of nasopharyngeal carcinoma, confirmed by core needle biopsy. All of the patients underwent an extension study with computed tomography scans of the neck, thorax, abdomen and pelvis to stage the tumour. In addition, in some cases[2] in which there were doubts about the extension of the disease, it was necessary to perform a positron emission tomography (Figs. 1 and 2).

The patients underwent multidiscipline management, which included chemotherapy followed by concomitant chemotherapy-radiation therapy. At the end of the treatment protocols, the response was assessed and the patients continued under close follow-up.

Because of a lack of means, it was not possible to carry out genetic tests to establish the relationship that existed between the genomic alterations and the HLA of the siblings diagnosed with nasopharyngeal carcinoma.

Results

Three families were identified in the period examined, with 2 members in each, for a total of 6 patients with a diagnosis of undifferentiated carcinoma of the nasopharynx (3 women and 3 men). The mean age was 46 years (range, 28–69). The familial relationship was the same in all of the cases (siblings). Average follow-up was 10 years and 3 months (range, 8 months to 23 years). All of the cases were of the Caucasian race. Involvement of EBV was established in only 3 of the cases, due to the fact that such testing was not routinely carried out in our hospital before 2005. The staging in all of the cases was advanced, given that there was ganglion involvement (5 cases), and only in 1 case was it N0, but it was T4 nonetheless; factors of poor prognosis in all of the