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Morphopathological study of naturally occurring ovine pulmonary adenocarcinoma in sheep in Fars province, Iran

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Summary

Ovine pulmonary adenocarcinoma (OPA) is a contagious and transmissible lung cancer of sheep resembling human bronchiolo-alveolar carcinoma. In the present study, lungs of 9400 sheep slaughtered in Fars province, Iran were examined morphopathologically. The OPA was diagnosed in the lungs of 21 (0.22%) out of 9400 sheep. Frequency of involvement of different lobes in the affected lungs was included apical lobe (62%), cardiac lobe (33%), middle lobe (33%), diaphragmatic lobe (62%) and accessory lobe (5%). In 12 sheep, the classical form observed as firm, white to grayish coalescing masses mostly in the cranio-ventral lobes associated with wet cut surface and frothy fluid in the airways. In 9 sheep, atypical lesions observed as small clearly demarcated nodules mostly in diaphragmatic lobes associated with dry cut surface and minor fluid in the airways. Histopathological changes were almost similar in the two forms. They consisted of an acinar or papillary growth of neoplastic cells in the alveoli and polypoid proliferation of bronchiolar epithelium. There were variable amounts of connective tissue, myxomatous foci and infiltration of lymphocytes and plasma cells in the interstitial tissue of the affected alveoli. No metastatic lesion was observed in the lymph nodes. The findings of this study show that atypical and classical forms represent different stages or manifestations of a single disease spectrum.

Key words: Ovine pulmonary adenocarcinoma, Morphopathology, Classical form, Atypical form

Introduction

Ovine pulmonary adenocarcinoma (OPA) is a contagious lung cancer of sheep also known as pulmonary adenomatosis, jaagsiekte (driving sickness), ovine pulmonary carcinoma and epizootic adenomatosis (De Martini and York, 1997; Palmarini and Fan, 2001; McGavin and Zachary, 2007). It is a retrovirus-induced spontaneous lung tumor of sheep that has striking analogies to some forms of human adenocarcinoma (Palmarini and Fan, 2001; Mornex *et al*., 2003). The etiologic agent of OPA, jaagsiekte sheep retrovirus (JRSV) is the only virus known to cause a naturally occurring lung adenocarcinoma. The incidence of the disease is usually 2-5% but in some flocks can reach to 30%. On the basis of a slaughterhouse study in Chahar Mohal Bakhtiari province of Iran, Kojouri and Karimi (2002) reported the disease occurrence of about 3% in sheep more than 3 years old. In an affected flock, the disease can be responsible for more than 50% of the mortality (Sharp and Angus, 1990). Affected sheep show an afebrile respiratory illness associated with loss of weight. Two pathological forms of OPA are recognized including classical and atypical (De las Heras *et al*., 1992; Garcia-Goti *et al*., 2000). The aim of the present study was to define morphopathological characteristics of two classical and atypical forms of naturally occurring OPA in native sheep of Iran.

Materials and Methods

Lungs from 9400 slaughtered native breed sheep were examined grossly in two

slaughterhouses in Fars province. The animals were nearly between 7-month- to 6-year-old. Pathologic lesions of 70 suspected lungs and associated mediastinal lymph nodes were recorded in pneumograms. Twenty-first out of 70 lungs were diagnosed as ovine pulmonary adenocarcinoma. Morphopathological studies were performed on 12 lungs with lesions of classical form and 9 lungs with lesions of atypical form. For detecting the frequency of different lobes involvement, the number and location of lesions were noticed. Gross appearance of lesions, particularly in cross section was studied comparatively. Multiple samples about 0.5-1 cm in diameter from each lungs and mediastinal lymph nodes were taken for microscopic examination. The samples were fixed in 10% neutral-buffered formalin, processed routinely, sectioned at 5 µm and stained with haematoxylin and eosin.

Results

The gross lesions in the affected lungs were characterized by focal to multifocal consolidated masses in the cranio-ventral or diaphragmatic lobes. They were greyish-white and usually variable in size, about 1-7 cm in diameter.

Frequency of involvement of different lobes was included apical lobe (62%), cardiac lobe (33%), middle lobe (33%), diaphragmatic lobes (62%) and accessory lobe (5%).

In 12 lungs, the classical form of OPA was observed usually with lesions located in the cranio-ventral portion. These lesions were seen as solitary or multiple firm masses about 2-7 cm in diameter surrounded by emphysematous lung tissue. The cut surfaces were moist with exuding serous frothy fluid from it. In some lungs, several lesions tended to coalesce to form larger masses with firm consistency (Fig. 1). The cut surface of these lesions was also moist and frothy fluid filled major airways, especially in the tracheal lumen.

In 9 lungs, atypical form of OPA was observed as subpleural located nodules in the dorsal aspects of diaphragmatic lobes. The lesions were focal or multifocal, relatively well circumscribed, greyish-white color as small hard nodules with about 1-4 cm in diameter. The cut surface of lesions was mostly dry without remarkable fluid in the airways (Fig. 2).

Histopathological changes were almost similar in two forms and in all 21 affected lungs. In the affected areas, the lesions were nonencapsulated and the alveoli were lined by neoplastic cuboidal to columnar cells. Two main growth patterns of tumor cells were observed including acinar or glandular and papillary (Fig. 3). In addition, papillary and polypoid proliferation of bronchiolar epithelium that filled the lumen were seen (Fig. 4). Neoplastic cells were well differentiated and mitotic index was not remarkable. There were a variable amounts of loose to dense connective tissue and mild to moderate infiltration of lymphocytes and plasma cells in the interstitial tissue of the affected areas. Numerous macrophages were observed mostly within less affected or apparently normal alveoli near to affected alveoli. Nodular foci of myxomatous tissue were found in the interstitial tissue of the affected areas. Lymphoid proliferation was seen inconsistently around the bronchioles and rarely lymphoid foci were present in the affected interstitial tissue. No metastatic lesion was observed in the mediastinal lymph nodes of any of the affected animals.

Discussion

Ovine pulmonary adenocarcinoma is of biomedical importance and is a substantial economic problem to sheep producers worldwide (Sharp and Angus, 1990). OPA has been classified as a bronchioalveolar carcinoma resembling human bronchioalveolar carcinoma (Nobel and Perk, 1978). However, the classification by the World Health Organization (WHO) of human lung tumors gives a more stringent definition of bronchiolo-alveolar carcinoma (Travis *et al*., 1999; Palmarini and Fan, 2001). This is a morphopathological description of classical and atypical forms of OPA in sheep in Iran. The pathological manifestations of classical form of the disease was reported by several researchers in the world (Cutlip and Young, 1982; De Martini *et al*., 1985; Sharp and Angus, 1990;

Verwoerd, 1990; Bouljihad *et al*., 1996; Kojouri and Karimi, 2002).

Although, classical form of pulmonary adenomatosis had been well-recognized, until 1992 there was not any classification about different morphopathological features of OPA in the literature. For the first time, De las Heras *et al*. (1992) reported the occurring of two pathological forms including atypical and classical in the course of abattoir studies in Spain. After that, the term of atypical form is used in reports and both classical and atypical forms are identified sometimes even in the same flock (Garcia-Goti *et al*., 2000; Sharp and De las Heras, 2000). In the present study, pathologic changes to some extent were consistent with either the classical or atypical forms of OPA. Therefore, these two forms were studied comparatively in naturally occurring cases.

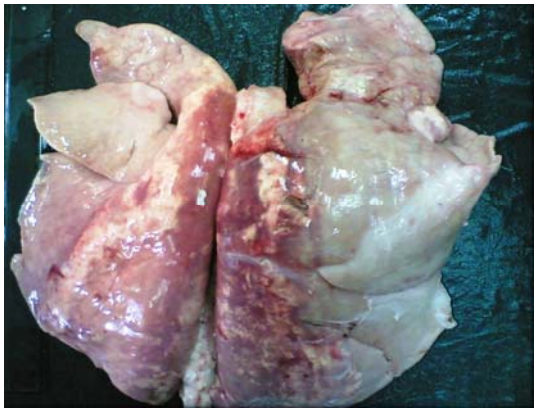

Fig. 1: Classical form, OPA, sheep. Widespread consolidated greyish-white areas in the cranial and caudal lobes of lungs

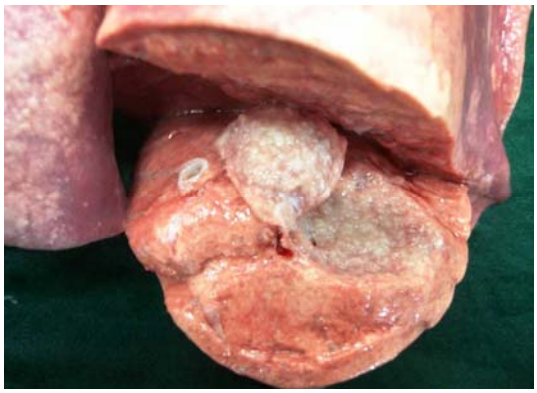

Fig. 2: Atypical form, OPA, sheep. Cut surface of tumoral lesion shows whitish dry nodule without fluid in the airways

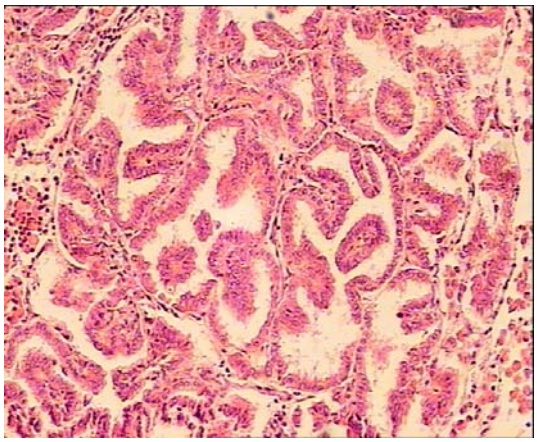

Fig. 3: Main histopathologic patterns of OPA. Affected alveoli lined by neoplastic epithelial cells with acinar and papillary growth, (H&E, ×200)

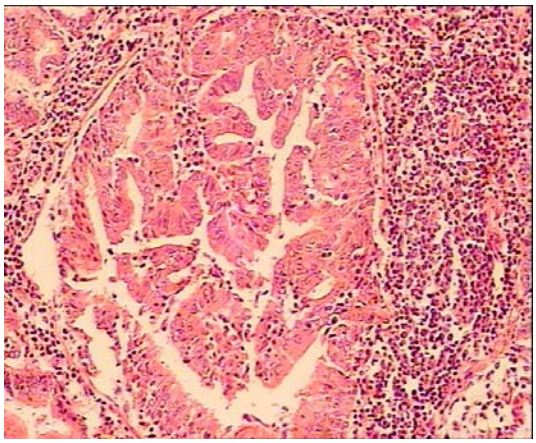

Fig. 4: OPA, sheep. Remarkable proliferation of bronchiolar epithelium associated with prominent peribronchiolar lymphoid tissue, (H&E, ×260)

Metastasis to mediastinal lymph nodes were not observed in the present study. This is in agreement with some reports (Sarkar *et al*., 1988; Verwoerd, 1990; Bouljihad *et al*., 1996; Uzal *et al*., 2004) but differs from those reported intra or extra-thoracic metastasis (Hunter and Munro, 1983; Synder *et al*., 1983; Verwoerd *et al*., 1985; Nobel *et al*., 1969; De las Heras *et al*., 2003). William and Yates (1988) reported metastasis in the mediastinal lymph nodes and kidneys; renal and cardiac metastases of OPA-like tumor was also reported by Al-Dubaib (2005) in a goat. There is no explanation to clarify this discrepancy. The ability of OPA tumors to metastatize and the capacity of OPA tumor cells and derived cell lines to transplant in nude mice indicate that the nature of lesions is neoplastic rather than proliferative,

although the majority of lesions have a hyperplastic phenotype (Palmarini and Fan, 2001).

In this study, the presence of small foci of myxomatous connective tissue between the affected alveoli in the interstitial tissue was resembled those described by others (Cutlip and Young, 1982; De Martini *et al*., 1985; Sharp and Angus, 1990; Bouljihad *et al*., 1996; Kojouri and Karimi, 2002). The origin of the myxomatous foci and its relation to JSRV infection is still unclear.

Infiltration and accumulation of mononuclear inflammatory cells mostly lymphocytes and plasma cells and also variable amount of loose to dense fibrous connective tissue were seen in the interstitial tissue of neoplastic foci in both forms of OPA. Our results show these reactive changes in the tumor stroma which seems to be due to a specific immune response of the host not to concurrent infections.

In this study, accumulation of macrophages within apparently normal alveoli beside affected alveoli was a prominent feature in the tumor. This is in agreement with other reports (Rosadio and Sharp, 1992; De las Heras *et al*., 1995; Garcia-Goti *et al*., 2000; Kojouri and Karimi, 2002; Platt *et al*., 2002; Summers *et al*., 2005). The immune response to JSRV is poorly understood. Summers *et al*. (2005) reported that an influx of macrophages is the predominant local immune response in OPA.

Morphopathological findings of classical and atypical forms of OPA in this study support the hypothesis that these two forms represent the different stages or manifestations of a single disease spectrum (Garcia-Goti *et al*., 2000; Uzal *et al*., 2004).

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