Identification of atypic and classic, mucinous and nonmucinous forms of ovine pulmonary adenocarcinoma (OPA) and TTF1 marker expression

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Abstract:

BACKGROUND: Ovine pulmonary adenocarcinoma (OPA) is a worldwide contagious bronchioalveolar carcinoma caused by infection of a beta retrovirus in sheep and less in goat. Neoplastic proliferation of type II pneumocytes and clara cells, produce papillary to acinar tumoral pattern with infiltration of macrophages, lymphocytes and plasma cells and interstitial fibrosis tissue. **OBJECTIVES:** This study was conducted to investigate the patterns of OPA and check the expression of TTF1. **METHODS:** A total of 7952 ovine lungs were studied for macroscopic and microscopic pathology examination and so, to check TTF1 marker. **RESULTS:** 25 cases were diagnosed as OPA and, based on macroscopic and histopathologic lesions, two different classifications were defined. Tumoral lesions were divided to classic (68%) and atypic (32%) forms of OPA based on growth pattern and progression and two other forms of mucinous (56%) and non-mucinous (44%) OPA based on histologic characterization of neoplastic secretory cells were descripted. 6 out of 8 examined cases for TTF1 marker staining, were positive and 2 cases were negative in immunohistochemical test. **CONCLUSIONS:** Two forms of classic and atypic lesions and so mucinous and non-mucinous forms were found. The classic form was more than the atypic and the mucinous form was more than non-mucinous lesions. TTF1 marker expression revealed the pulmonary origin of tumors.

Introduction

Ovine pulmonary adenocarcinoma (OPA) is a contagious retroviral bronchioalveolar carcinoma in sheep that is rarely observed in goats. It is a financially significant disease. More than 80% of the herd might be wasted at the first encounter with the virus and up to 20% of the herd might be infected on average. No effective treatment or vaccine is readily available to control and eradicate this disease. It is known as a worldwide disease with infectious origin. The etiology of this neoplasm is based on a beta retrovirus of retroviridae family. There is not any oncogenic agent in the virus and it has been shown that the envelope protein of the virus is enough to induce the tumor (Palmarini and Fan, 2001; Martineau et al., 2010; Jubb, Kennedy and Pulmer´s, 2007). The histo-

logical feature of this tumor is differentiated carcinoma in bronchioloaveolar tissue. Columnar or Cuboidal epithelial neoplastic cells cover the airways and lead to papillary or acinar structures. Alveolar walls in these neoplastic masses are covered by Columnar or Cuboidal epithelial neoplastic cells. These structures fill the alveolar spaces and obstruct their ways and alveoli surrounding neoplastic area. The adjacent alveoli show atelectasis. Macrophages are abundant in alveoli. There is interstitial fibrosis in severe cases. Neoplastic cells show type II pneumocyte phenotype including cytoplasmic lamellar bodies and surface microvilli. Less commonly, dense granules might be seen in these cells and phenotype indicates Clara cell structure. These specifications explain the form of bronchioloalveolar carcinoma tissue (Jubb, Kennedy and Pulmer´s, 2007 - Khodakaram-Tafti and Hematian 2011 - Martineau et al., 2010 - Beytut et al., 2009 - Bahari et al., 2016). Prevalence of the disease in slaughterhouses of sheep over three years old has been estimated about 3 percent in Chaharmahal and Bakhtiari Province (Kojouri, and Karimi, 2002). A study was conducted on tracing the virus in Fars Province by RT-PCR showed that the virus was detected in all infected lungs (Khodakaram-Tafti et al., 2009). Pulmonary adenomatosis has been detected in 4 goats in Khuzestan province microscopically and histopathologically (Sayyari and Mohamadian ,2012). Infection was highly prevalent in the northwest of Iran and controlling it seems very important (Rezazadeh et al., 2012).

Materials and Methods

The tissue specimens were collected for about one year, accidentally and weekly from one industrial slaughterhouse in Shahryar township of Tehran province. In this survey 7952 specimens of sheep lungs were studied. The lungs with macroscopic lesions which were suspected to be involved with adenocarcinomatous lesions accompanied by mediastinal lymph nodes were taken and fixed in 10% neutral buffered formalin solution. The tissues were passaged and imbedded in paraffin blocks, sectioned at 5 micron thickness and finally stained with hematoxylin and eosin method. 8 cases of tissues were chosen for immunoreactive staining of TTF1 marker by avidin-biotin-peroxidase complex method using the DAKO kit, to determine whether the tumor is primary or metastatic form of carcinoma in lung. Tissue sections were studied histopathologically by two pathologists for evaluation of nuclear expression of protein.

Results

Macroscopic Observations: From 7952 cases, 27 lung specimens had macroscopic appearance similar to that characteristic of pulmonary adenomatosis. By histological examination 25 cases were detected as adenocarcinoma bronchioalveolar structure. There were focal and multifocal hard and bulging lesions, with grey to white or purple colors. In some samples, the involved areas were harder, white to grey and without production of lung fluid. In many other cases excessive production of lung fluid was observed.

In the samples of this study, cranioventral areas were mostly involved. However, in some cases, the infection was more severe and scattered in lung tissue. In other cases,

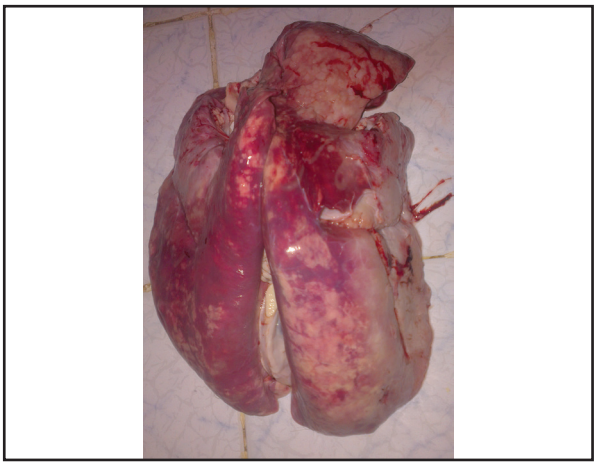

Figure 1. Pulmonary adenocarcinoma, dorsal and lateral view of ovine lung. Diffuse enlarged, grey to purple, edematous lesions.

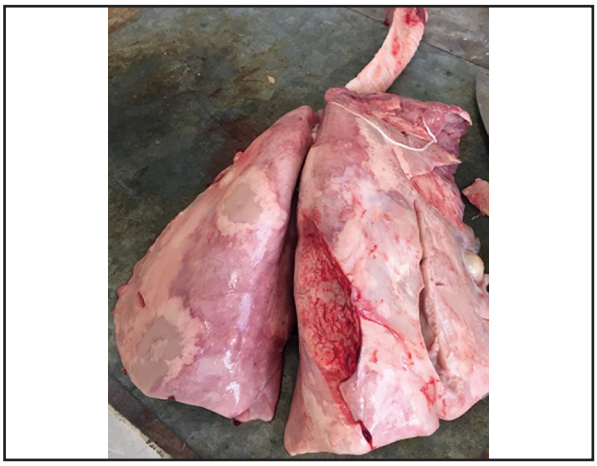

Figure 2. Demarcated white greyish nodules of various size in lung lobes.

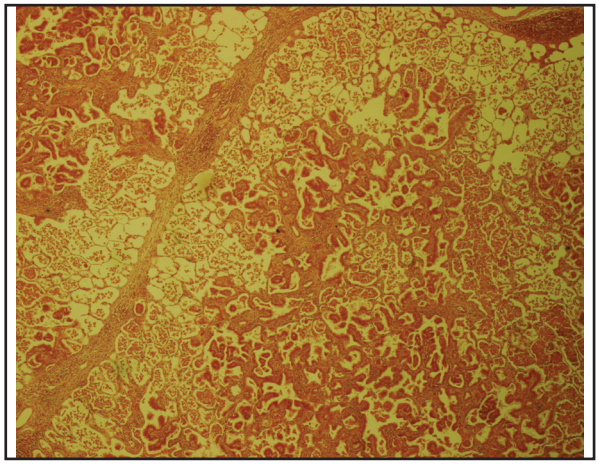

Figure 3. Neoplastic growth of epithelial cells in pulmonary alveoli and infiltration of alveolar macrophages in classical form of OPA, sheep lung. (H&E)(x40).

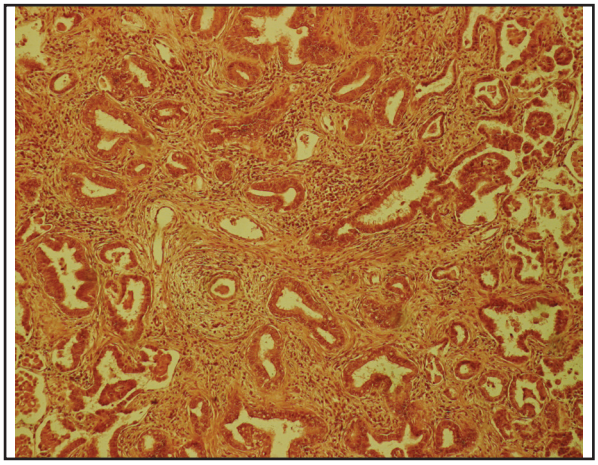

Figure 4. Neoplastic alveoli with proliferative connective tissue (fibrosis) and infiltration of mononuclear cells in atypical form of OPA, sheep lung. (H&E)(x100).

central necrosis and hemorrhage in tumoral areas were observed.

In 17 cases, heavy and large focal masses of white and grey color and some in purple, about 2 to 10 centimeters in diameter, surrounded by emphysematous parenchyma were observed. In some samples, several tumoral foci were joined together to form larger areas. Cross-cutting surfaces of these samples were moist with serous and foamy secretions on airways and parenchyma. These samples were categorized as classical OPA (Fig. 1).

In 8 samples single firm masses with few secretions in white to greyish about 3 to 7 centimeters in diameter were seen and were categorized as atypical OPA (Fig. 2).

Histopathological Findings: The samples were categorized into two forms of classical and atypical. The histopathological form of the classic adenocarcinoma presents small and large encapsulated neoplastic nodules with columnar to cuboidal cells in papillary to acinar growth. There was no sign of invasion. In most cases, large macrophages were seen in alveoli (Fig. 3). Histopathology of atypical adenocarcinoma is similar to classical forms except that

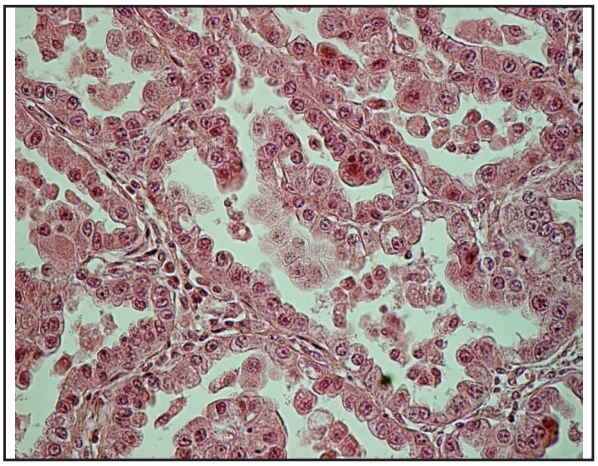

Figure 5. Acinar and papillar appearance of neoplastic alveoli with short cuboidal epithelial cells in classical non-mucinous form of OPA, sheep lung. (H&E)(x200).

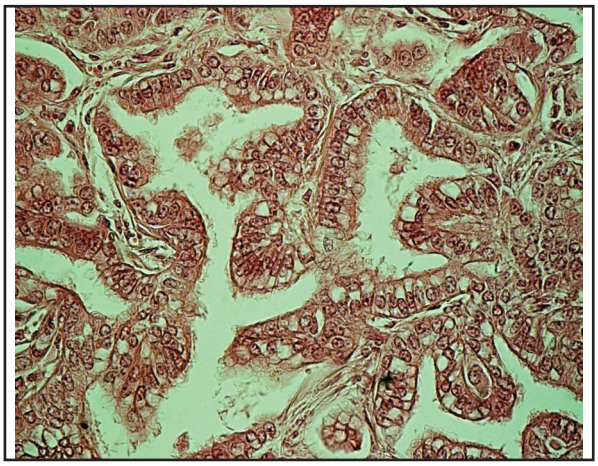

Figure 6. Neoplastic columnar cells with typical cytoplasmic mucin droplets lining alveoli, acinar to papillar growth related to classical mucinous form of OPA, sheep lung. (H&E)(x400).

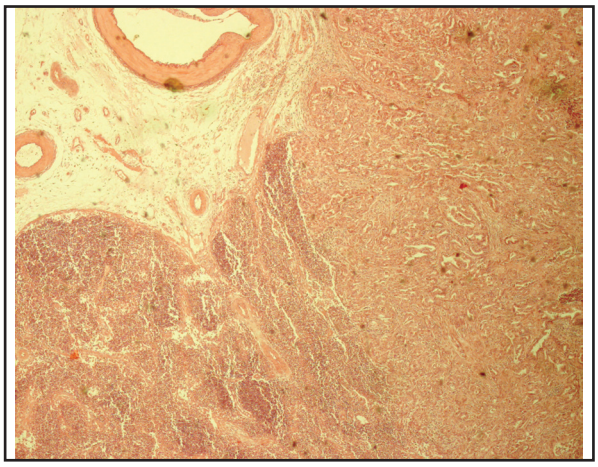

Figure 7. Mediastinal lymph node metastasis of OPA affected tissue, sheep mediastinal lymph node. (H&E) (x100).

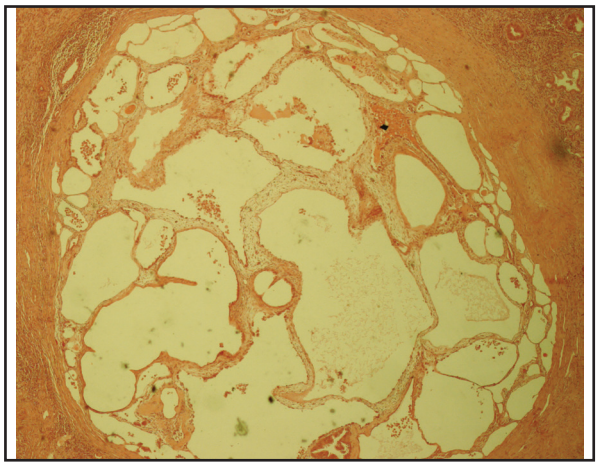

Figure 8. Cyctic growth of neoplastic epithelial cells and mucin secretion in OPA affected pulmonary tissue, sheep. (H&E)(x40).

neoplastic foci are often smaller and more limited in classic form. Severe infiltration of mononuclear cells and fibrosis can be seen in surrounding areas (Fig. 4). Macrophages and plasma cells are abundant in alveolar and interstitial spaces.

Another classification divides OPA into mucinous and non-mucinous forms. Non-mucinous adenocarcinomas are characterized by short columnar to cuboidal cells lining neoplastic alveolar walls (Fig. 5). Mucinous adenocarcinomas have long cylindrical cells with foamy cytoplasm filled with mucin secretions that push the nucleus to the cell border (Fig. 6). Invasion of tumoral cells from basal layers to lower layers were few in cases of the present study.

From 24 Adenocarcinomas of our study, just one Mediastinal lymph node metastasis was observed (Fig. 7). The neoplastic cells of this case were characterized by varying sizes, degrees of pleomorphism, big and bright nuclear and clear nucleoli. Mitotic figures were more significant.

Small and big cysts were observed in 4 lung tissues. Cyst walls were covered by columnar to cuboidal neoplastic cells. Mu-

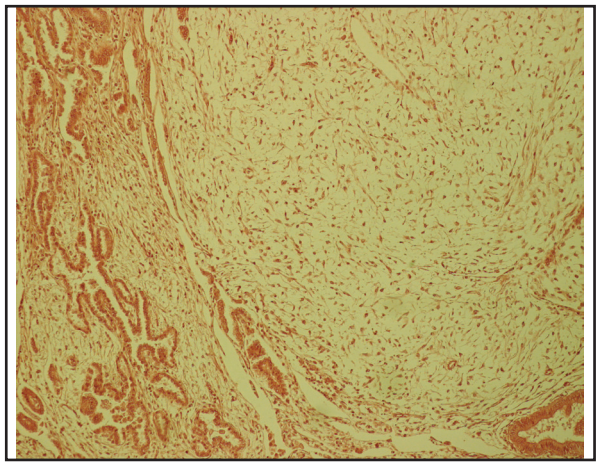

Figure 9. Myxoid tissue in OPA affected pulmonary tissue, sheep. (H&E)(x400).

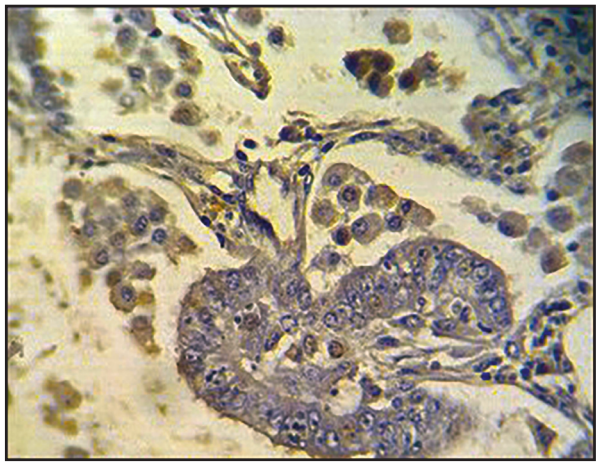

Figure 10. Immunohistochemical finding of Thyroid Transcription Factor (TTF-1) marker expression in neoplastic nuclei showing nuclear immunoreactivity. (x400).

cin secretions were also observed inside the cysts (Fig. 8). Three cases had shown some myxoid tissue in interstitial space of neoplastic alveoli (Fig. 9).

Big foamy macrophages were abundant in alveoli, which are more obvious in classic forms. Plasma cells and other mononuclear cells could be seen in tumoral and even non-tumoral interstitial space, while they were more frequent in atypical forms. Necrosis and severe infiltration of neutrophils were observed at some part of tumoral parenchyma.

Severe infiltration of mononuclear lymphocytes into the alveolar walls was seen in some tissue samples and even their mitosis division can be signs of simultaneous occurrence of pulmonary adenomatous and Maedi disease.

6 out of 8 examined cases for TTF1 marker staining were positive and 2 cases were negative for immunohistochemical test (Fig. 10).

Discussion

Ovine pulmonary adenocarcinoma is one of the many reasons of respiratory failure and pneumonia in sheep and less in goats. There have been some previous studies in other regions of Iran on the prevalence of this disease. In a period of six months in Khuzestan, a study was conducted on 3985 goats in which four goats showed macroscopic and histopathological lesions related to classic OPA (Sayyari and Mohamadian, 2012). In one study that was conducted in Fars province on lungs of 9400 sheep, 21% were diagnosed as OPA and showed both classical and atypical forms without any metastasis (Khodakaram-Tafti and Hematian, 2011). According to another study on lung tissues with OPA in Fars province, JSRV was detected by RT-PCR in all cases of suspected lungs (Khodakaram-Tafti et al., 2009). Another study in the northwest of Iran on the outbreak of pulmonary adenocarcinoma, and among 167 samples, 30 samples were positive. Finally, it was shown that this infection is highly prevalent in this part region of the country (Rezazadeh et al., 2012).

In the present study, from 7952 ovine lung tissues in a slaughterhouse during one year, 25 cases were positive histopathologically, indicating that the outbreak in that area was about 0.3 %.

According to available reports, there are two forms of OPA, including classical and atypical adenocarcinoma that could be identified clinically and histopathologically. Classical forms are often progressive to death while atypical forms remain subclinical. Histology of two forms is also similar, with the difference being that in the atypical form, infiltration of mononuclear cells, particular lymphocytes and plasma cells, and connective fibers to stromal are more (Martineau and Cousens Griffiths, 2010 - Summersa et al., 2012).

Some samples had different histological characteristics that indicate the intermediate state of classical and atypical forms or they are progressing neoplasms. Two cases of classic OPA explained small and large cysts with neoplastic cells. In mucinous form, long columnar cells were lining the alveoli walls with abundant cytoplasmic mucin and basal nuclei. In Non-mucinous forms, Clara cells and pneumocytes grow on alveolar wall and there was no stromal invasion (Palmarini and Fan 2001). In this study, mucinous forms were long cells with light and foamy cytoplasm, mucin secretion, acinar and papillary growth. In some parts of tissues, there were frequent large neoplastic cells and they filled alveoli. In non-mucinous forms short cells with pink cytoplasm were usually arranged in the walls of the alveoli. In some of the lesions both mucinous and non-mucinous forms existed. Furthermore, in two cases of lung lesions, some myxomatous nodules were observed.

One of 25 tumoral cases (4%), metastasized to mediastinal lymph node. This tumor was highly malignant with severe polymorphism, large nuclei, clear nucleoli with frequent mitotic figures. Usual organs for metastasis of OPA cells are intrathoracic metastases in the diaphragm, chest wall, heart and lymph node and metastases outside the chest area in the liver, kidney, adrenal glands, skeletal muscle, skin, digestive tract and spleen (Minguij_on, 2013).

TTF-1 (Thyroid transcription factor-1) expression is useful in distinguishing pulmonary from nonpulmonary tumors (Agoff, N.S., et al.). TTF-1, a nuclear protein, plays a role in transcriptional activation during embryogenesis in the thyroid, diencephalon, and respiratory epithelium (Bohinski RJ.,et al 1993 - Lazzaro D, et al,. 1991). In 6 out of 8 cases of our study, TTF 1 positive staining revealed pulmonary origin of these neoplasms.

Histological similarities between OPA and human lung tumors have been recognized for many years (Bonné, 1939), and OPA is regarded as a natural animal model for human lung adenocarcinomas of mixed subtypes (De las Heras et al., 2003 - Mornex et al., 2003 - Palmarini and Fan, 2001). A retroviral etiology for these human tumors has been suggested, and some cases have been shown to express an antigen related to betaretroviral Gag proteins (De las Heras et al 2000 - De las Heras, M., et al. 2007 - Hopwood et al., 2010). However, additional markers of retroviral infection in these patients have not been found (Hopwood et al., 2010). Antigen expression of virus Gap that causes lung adenocarcinoma is verified in some human tumors, but other evidence of beta-retroviral infections have not been observed. It is also shown that although the virus is present in human lung tumors, these viruses are not associated with beta-retrovirus. Other immunohistochemical studies suggest that some human lung carcinoma including bronchial alveolar carcinoma can be associated with JSRV retrovirus but no

molecular study has been done to stabilize the expression (Hopwood et al., 2010).

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تعیین اشکال آتیپیک و کلاسیک، موسینی و غیر موسینی و بیان ژن TTF۱ در کارسینوم ریوی گوسفند

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چکیده

زمینه مطالعه: آدنوکارسینوم ریوی گوسفند (OPA)، کارسینوم برونشیوآلوئولار قابل انتقال با وسعت جهانی می‌باشد که از طریق عفونت با یک بتا رتروویروس در گوسفند و کمتر بز ایجاد می‌شود. تکثیر نئوپلاستیک سلول های پنوموسیت تیپ II و سلول‌های کلارا، ساختارهای توموری پاپیلاری تا آسینی شکل به همراه نفوذ ماکروفاژ، لنفوسیت و پلاسماسل و همچنین فیبروز بینابینی ایجاد می کند. **زمینه مطالعه:** این مطالعه با هدف بررسی الگوهای آدنوکارسینوم ریوی گوسفند و چگونگی بیان مارکر TTF۱ انجام گرفته است. **روش کار:** تعداد ۷۹۵۲ نمونه ریه گوسفند مورد مطالعه ماکروسکوپیک و میکروسکوپیک پاتولوژی و همچنین بیان مارکر TTF۱ قرار گرفته است. **نتایج:** ۲۵ مورد آدنوکارسینوم ریه تشخیص داده شد که براساس خصوصیات ماکروسکوپیک و هیستوپاتولوژیک، دو تقسیم بندی مختلف صورت گرفت. ضایعات توموری، براساس الگوی رشد و درجه پیشرفت، به دو فرم کلاسیک (۶۸٪) و آتیپیک (۳۲٪) و براساس خصوصیات هیستولوژیک سلول‌های ترشحی نئوپلاستیک، به دو فرم موسینی (۵۶٪) و غیر موسینی (۱۴٪) دسته بندی شدند. ۶ مورد از ۸ مورد نمونه مورد بررسی ایمنوهیستوشیمیایی مارکر TTF ۱، نتیجه مثبت و ۲ نمونه نتیجه منفی نشان دادند. **نتیجه گیری نهایی:** دو فرم کلاسیک و آتیپیک و همچنین دو فرم موسینی و غیرموسینی آدنوکارسینوم ریه گوسفند تشخیص داده شد. فرم کلاسیک بیش از فرم آتیپیک و فرم موسینی بیش از فرم غیرموسینی بود. بیان مارکر TTF۱، نشان دهنده این بود که این تومورهای مورد مطالعه، اولیه و با منشا بافت ریه بود ه و متاستاتیک نمی‌باشند.

واژه های کلیدی: آدنوکارسینوم، گوسفند، پنوموسیت، ریه، رتروویروس

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