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The Role of Mutations on Genes ASPSCR1 & TFE3 in Alveolar Soft Part Sarcoma

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Abstract

Soft alveolar sarcoma (ASPS) is a rare, slow-growing tumor in alveolar soft tissue whose cause is unknown. This is one of the few cases of sarcoma that represents 1.2-1% of large studies of soft tissue sarcomas. ASPS is classified as a soft tissue sarcoma. Sarcomas are malignant tumors that arise from connective tissue, which connects, supports, and surrounds various structures and organs in the body.

Key Words: alveolar soft sarcoma (asps); aspscr1 gene; tfe3 gene; cancer; genetic mutations

Generalities of Alveolar Soft Sarcoma (ASPS):

Soft alveolar sarcoma (ASPS) is a rare, slow-growing tumor in alveolar soft tissue whose cause is unknown. This is one of the few cases of sarcoma that represents 1.2-1% of large studies of soft tissue sarcomas. ASPS is characterized by a painless mass that usually forms in the legs or buttocks, with a specific tendency to shift to the lungs as multiple nodules, possibly while the sarcoma itself is still small. This disorder is very rare because it involves a special fracture and connection between two chromosomes called "unbalanced displacement." This finding is basically seen in all the people who have been examined so far. This disorder cannot be passed on to the offspring of the next generation because it occurs only in tumor cells and not in normal cells. In addition, there is no family in which multiple family members have the disorder. ASPS is more common in young people, especially adults and young people [1].

Surgical treatment is the main site of sarcoma. Radiation therapy is sometimes considered as an adjunct to surgery depending on the nature of the tumor (size, location, microscopic shape). For a disease that goes to the lungs, surgery to remove the nodules is sometimes possible, but often chemotherapy is the only treatment option. However, this tumor tends to resist traditional chemotherapy, so intermittent approaches including newer "targeted" chemotherapy drugs are also a good option for treatment. Several new targeted therapies have been studied in clinical trials and are promising, but more research is needed on their safety and effectiveness. [1,2]

ASPS is classified as a soft tissue sarcoma. Sarcomas are malignant tumors that arise from connective tissue, which connects, supports, and surrounds various structures and organs in the body. Soft tissue includes fat, muscle, nerves, tendons, and blood and lymph vessels. [1,2]

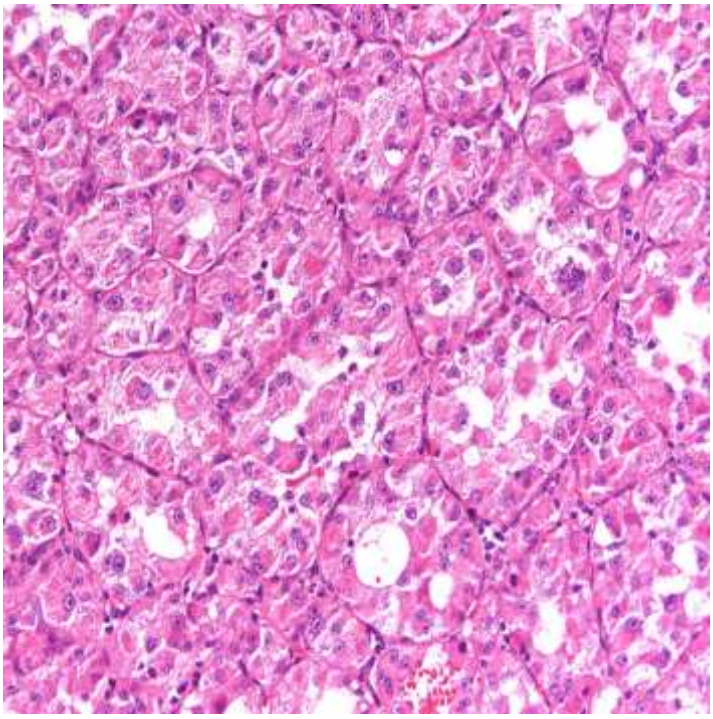

Figure 1: Microscopic image of a tissue sample with soft alveolar sarcoma. [1]

Clinical Signs and Symptoms of Soft Alveolar Sarcoma (ASPS):

Typical clinical findings are painless masses in the thighs and buttocks, although ASPS can occur in the trunk, arm, or elsewhere. Sometimes these masses cause pain due to stretching of the surrounding tissues and cause lameness or other difficulty in movement. These masses are usually soft and slow growing. In children, these lumps often occur on the head and neck, usually the tongue and eye sockets. In adults, the thighs and buttocks are often affected. [1,3]

Although ASPS is a slow-growing tumor, it can spread to other parts of the body (metastasize). Sometimes there is a significant delay years after the original tumor is removed, before the site of spread (metastases) can be identified. Lungs, brain and bones are most often affected by cancer. In the advanced stages, when nodules are found in the lungs, tumor nodules can cause coughing, severe chest pain, or accumulation of fluid around the lungs (pleural effusion). Some people experience headaches associated with metastasis to the brain or fractures of the bones due to metastasis. Lung or brain involvement with ASPS can have potentially life-threatening complications, but people can live with lung nodules for several years because the nodules grow very slowly for most people. In people with brain metastases, surgery and radiation therapy are the main ways to control the tumor and its side effects in the brain. [1,3]

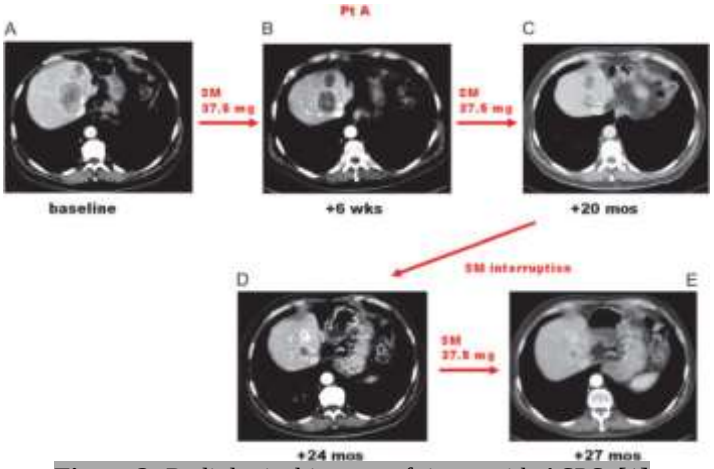

Figure 2: Radiological images of tissue with ASPS. [1]

Etiology of Soft Alveolar Sarcoma (ASPS):

So far, no external infectious agent has been identified that causes ASPS. It has been shown that in this disease, two chromosomes are broken and reconnected (unbalanced displacement), during which two genes that are normally located on the sex chromosome X and number 17 are physically mutated. [1,4]

Chromosomes are located in the nucleus of human cells and carry each individual's genetic information. The cells of the human body normally have 46 chromosomes. Pairs of human chromosomes numbered from 1 to 22 are called autosomal (sexless) and sex chromosomes are identified by the symbols X and Y. Males have one X chromosome and one Y chromosome, and females have two X chromosomes. Each chromosome has a short arm called "p" and a long arm called "q". Most chromosomes are divided into many bands that are numbered. Numbered strips identify the location of thousands of genes on each chromosome. [1,4]

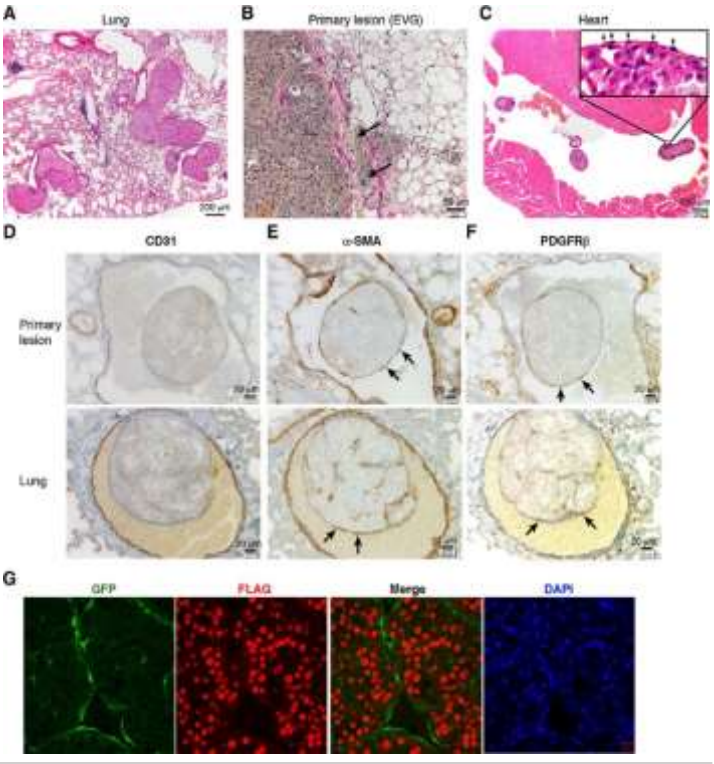

Figure 3: Microscopic and radiological images of tissues with ASPS. [1]

Two genes are involved in soft alveolar sarcoma, one of which is called ASPSCR1 gene, which is located in the long arm of chromosome 17 as 17q25.3, and the other gene is called TFE3, which is located in the short arm of the sex X chromosome as Xp11. 23 is located. In an unbalanced mutation, there is an unequal exchange between chromosomes that causes extra genes to be created or destroyed. In ASPS, the TFE3 gene is isolated from the sex X chromosome and attached to the ASPSCR1 gene on chromosome 17. This unbalanced transfer creates a new gene called "fusion" known as ASPSCR1-TFE3. This fusion gene synthesizes abnormal proteins. Researchers believe that this abnormal protein plays a significant role in the development of ASPS. However, more research is needed to determine exactly how this abnormal protein works. [1,5]

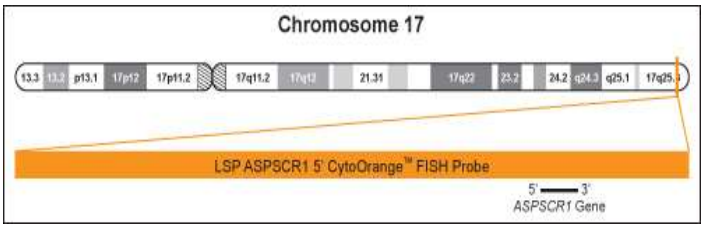

Figure 4: Schematic of chromosome 17 where the ASPSCR1 gene is located in the long arm of this chromosome as 17q25.3.[1]

Prevalence of Soft Alveolar Sarcoma (ASPS):

ASPS tend to affect young people, especially those between the ages of 15 and 35. It is rare in children under 5 years of age or in adults over 50 years of age. Women are more affected by the disease than men, especially under the age of 25. There seems to be no connection between this disease and a particular ethnic group. ASPS make up about 0.2-1% of all soft tissue sarcomas. Soft tissue sarcomas, in turn, make up about 1% of all cancers. [1,6]

Diagnosis of Soft Alveolar Sarcoma (ASPS):

Biopsy is the fastest way to diagnose soft tissue sarcomas. Sampling involves taking a small sample of damaged tissue and examining it under a microscope. There are more than 50 different types of sarcomas, with ASPS being just one rare subtype. Often, a core needle biopsy of the foot mass is sufficient for diagnosis. If core needle biopsy is not diagnostic, then sampling the section that acquires more tissue will make the diagnosis. [1.7]

Physicians can use biopsy specimens to examine cells to see if there is a characteristic change in the chromosome (an unbalanced mutation involving chromosomes 17 and X that leads to the formation of a fusion gene) (ASPSCR1-TFE3). This change confirms the ASPS diagnosis. Because the tumor grows slowly and usually does not cause obvious symptoms, people with the disease often develop ASPS years before diagnosis [1,7].

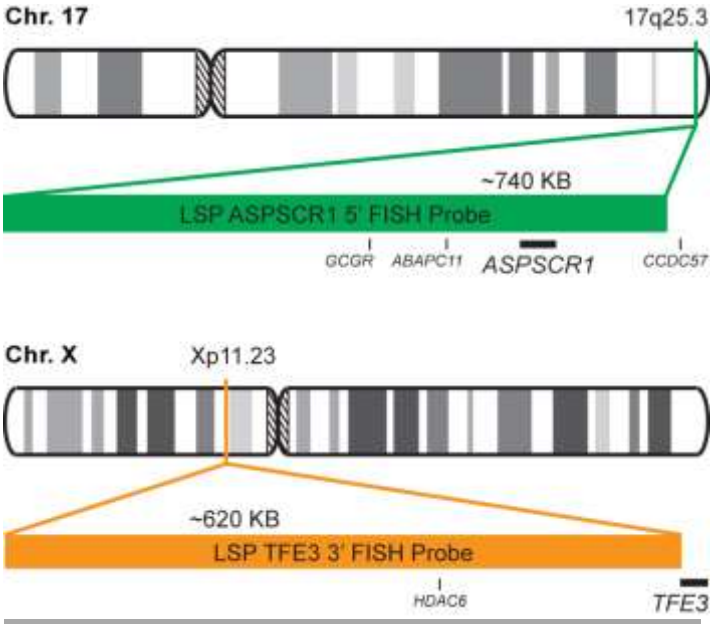

Figure 5: Schematic of the fusion of ASPSCR1 genes with TFE3.[1]

Typically, physicians also use specialized imaging techniques such as computed tomography (CT) scans or magnetic resonance imaging (MRI) scans of the primary tumor site. A chest CT scan is usually done to check for lung disease. Additional scans may also be done to assess the spread of the cancer to other areas of the body. ASPS are not generally transmitted to the lymph nodes, but instead prefer to circulate through the bloodstream to reach the lungs or other parts of the body [1,8].

Treatment routes for Soft Alveolar Sarcoma (ASPS):

Therapeutic management of people with ASPS may require the coordinated efforts of a team of medical professionals such as physicians specializing in diagnosis (pathology) and cancer treatment (medical oncologists), radiotherapy specialists (radiotherapists), surgeons, oncology nurses and other specialists [1,8].

Specific treatment methods and interventions may vary, depending on several factors, including the location of the primary tumor, the extent of the primary tumor (stage) and the degree of malignancy (degree), whether the tumor has spread to distant locations, the individual's age, and general health; And / or other dependent elements. Decisions about using specific interventions should be made by physicians and other members of the health care team in close consultation with the patient, based on their characteristics [1,8].

Surgery is a standard treatment option for ASPS. However, the identification of the ASPSCR1-TFE3 fusion gene has opened up new avenues for treatment. Researchers are studying targeted therapies designed to prevent the effects of this abnormal gene
If the prognosis of the tumor is small and local (ie it has not spread to another part of the body, such as the lungs), it is better, and it can be completely removed with surgery. Amputation is rarely used as a surgical procedure to treat sarcoma (less than 5% of the time it occurs in most major sarcoma centers in the United States) [1,9].

Often, radiation therapy is used before or after surgery to minimize the chance of the tumor returning to the site of onset. This can be achieved by directing a beam of radiation to the tumor (external beam radiation or some other type of radiation) or by placing temporary catheters (tubes) in the area where the tumor has been isolated. These tubes protrude from the skin and can deliver the radiation beads that are placed in them to deliver a high dose of radiation to the tumor area in a very specific way. This method is called brachytherapy. When the tumor is 5 cm or larger in size, external beam radiation or brachytherapy is usually considered. For smaller tumors, it is not clear whether radiation helps reduce the risk of tumor recurrence [1,10].

Chemotherapy for ASPS after surgery (and radiation for some people), such as breast cancer or colon cancer, does not reduce the risk of tumor recurrence [1,10].

If the tumor is advanced and has spread (metastasized) or recurred, surgery is still sometimes considered, depending on the extent of the disease, especially the number of damaged points. For patients for whom surgery is not a viable option, chemotherapy is the only mainstay of treatment. However, traditional chemotherapy for metastatic disease has generally been ineffective. Standard drugs for sarcoma include doxorubicin and ifosfamide, but do not work well for ASPS. In a small number of people with ASPS who are treated with these drugs, the size of the tumors becomes smaller and if the tumor spreads beyond the site of the tumor, chemotherapy will not cure it. Given these limitations in traditional chemotherapy, most specialists in this field are quick to consider new or research treatments [1,10].

Discussion and Conclusion:

ASPS is characterized by a painless mass that usually forms in the legs or buttocks, with a specific tendency to shift to the lungs as multiple nodules, possibly while the sarcoma itself is still small. This disorder is very rare because it involves a special fracture and connection between two chromosomes called "unbalanced displacement." This finding is basically seen in all the people who have been examined so far [1,11].

Because the genes involved in this rare disease are already known, researchers are studying targeted therapies for ASPS. Targeted therapies prevent cancer from growing and spreading by targeting a specific gene, or proteins produced by those genes. Targeted therapies have fewer side effects than traditional chemotherapy because they "target" specific genes or proteins in cells. Traditional chemotherapy targets every dividing and growing cell in the body, even healthy cells. Several new drugs are currently being tested in clinical trials to treat people with ASPS. These include pazopanib, axitinib, pembrolizumab, cediranib, perifosine, and sunitinib [1,11].

Researchers are studying other new treatments for soft tissue sarcoma. These treatments include drugs such as angiogenesis inhibitors to prevent blood vessels from growing into tumors, new chemotherapy drugs, and immunological and biological therapies [1,11].

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