Article #2 (1.5 contact hours) Refereed Peer Review Email comments/questions to compendium@medimedia.com

Radiographic Signs of Pulmonary Disease: An Alternative Approach

Cornell University Stephanie G. Nykamp, DVM Peter V. Scrivani, DVM Nathan L. Dykes, DVM

ABSTRACT: Veterinary practitioners often have difficulty evaluating thoracic radiographs using the currently accepted paradigm of radiographic lung patterns. A different approach based on using radiographic signs to generate a differential diagnosis list and then using clinical signs to establish priorities within the differential list is described. The most important radiographic sign is location; determining the location of the opacity, similar to classification in gross pathology, is proposed as a more reliable and accurate method for generating a differential diagnosis list than is using the pattern of opacity detected.

special colloquium was held on the use of radiographic patterns of lung diseases during the 1996 American College of Veterinary Radiology annual scientific convention in Chicago. From the ensuing discussions, it was clear that a systematic approach to the radiographic diagnosis of pulmonary diseases is necessary. It also was evident that the current paradigm of using four patterns of increased fluid or soft-tissue opacity (i.e., alveolar, interstitial, bronchial, vascular) is cumbersome, difficult to learn, and subject to disagreement; nevertheless, it is the best approach currently available. Modifications and enhancement of the four basic terms (e.g., bronchointerstitial, peribronchial, hyperlucent, miliary, linear, reticular, nodular) have added to the confusion. In theory, the advantage of classifying diffuse pulmonary disease into patterns is that it helps establish specific diagnostic differentials.¹⁻³ Physician radiologists have recognized for years that the lack of agreement on patterns among radiologists is a definite disadvantage. This pitfall is so substantial that there are people in both human and veterinary medicine who feel the approach should be abandoned altogether.^{4,5} This lack of accord seems to be largely due to inconsistent use of the terminology that occurs when generalizing radiographic signs into patterns.⁶ The term *interstitial* creates a different image in each individual's mind; therefore, difficulties occur when communicating patterns among radiologists and private practitioners as well as students struggling to interpret pulmonary disease.4

CE

The currently accepted paradigm of using radiographic lung patterns to classify pulmonary disease is not universally agreed upon as the best method available to diagnose lung disease.

Traditional lung patterns are often mixed and, at best, reflect a difference in disease severity not the type of disease or histologic lesion localization.

Localizing disease to a level similar to gross pathology is the best classification that can be achieved with radiographs.





Figure 1—Lateral (A) and ventrodorsal (B) radiographs of a dog, demonstrating a diffuse mixed lung pattern (alveolar and interstitial). Interstitial pneumonia of unknown cause was diagnosed by histology. This illustrates the inconsistent correlation between the histologic lesion and the radiographic signs.

Figure 1A—Lateral

Additionally, there is poor correlation between the radiographic diagnosis of an interstitial or alveolar pattern and the histologic lesion (Figure 1).7 Anatomic pattern recognition makes the assumption that we can distinguish different microscopic lung structures radiographically. This assumption is likely naïve and incorrect because it presumes that disease processes are confined to a specific microscopic region. The interstitium includes the blood vessels, lymphatics, bronchioles, and alveoli and surrounds the major bronchi.^{8,9} Therefore, it is difficult to differentiate disease in the interstitium from disease in the alveoli and bronchi because the interstitium is intimately associated with all of these structures. Furthermore, presumably all diffuse pulmonary diseases have some interstitial component and they are unlikely to have a pure alveolar or bronchial pattern.^{2,4,7,9} Additionally, it is common to note that over time the pulmonary pattern expressed will vary, whereas at the microscopic level, the disease does not change location, only severity.^{10,11}

USING RADIOGRAPHIC SIGNS INSTEAD OF PATTERNS

Although Felson⁴ suspected that patterns of opacities often indicate specific diseases when he described the radiographic approach, a descriptive model based on the microscopic distribution did not facilitate clear communication of these findings. It became apparent that a more descriptive pulmonary pattern based on something other than subgross anatomy might be more useful and that precise and consistent terminology should be used to define these patterns and permit more accurate communication among radiologists.^{4,7} Describing the radiographic signs, rather than patterns, is proposed as an alternative system for describing pul-

Figure 1B—Ventrodorsal



Figure 2A—Lateral

Figure 2—Schematic drawing of the cranioventral and caudodorsal lung fields as seen on a lateral (A) and ventrodorsal (B) thoracic radiograph. The cranioventral lung field is light gray to represent disease. The presence of disease in the cranioventral lung field will obscure the cranial margin of the heart.



Figure 2B—Ventrodorsal

monary lesions. It is simpler, easier to teach, and equally or more meaningful than the currently used system. Radiographic signs are defined as visual cues, caused by a pathologic change in the tissue (or sometimes artifacts), that are detected in a radiograph. There



Figure 3A—Bronchopneumonia



Figure 3B—Noncardiogenic pulmonary edema

Figure 3—Radiographs demonstrating increased soft-tissue opacity that silhouettes with the pulmonary blood vessels in the cranioventral lung field (A) and caudodorsal lung field (B). A is a case of bronchopneumonia; B is a case of noncardiogenic pulmonary edema from chewing on an electrical cord. In both cases, the pattern of opacity is the same but the different locations of the opacity allow for refinement of the differential diagnosis.

are general radiographic signs that apply to all organ systems (i.e., size, shape, location, opacity, number, margination). There are also special radiographic signs that are unique to certain systems (e.g., airbronchogram, lobar sign). The best radiographic signs are highly sensitive and specific for a disease. A collection of radiographic signs is a pattern, and to conclude that a particular pattern is present, some or all of the signs of that pattern must be detected. This process relates to interpreting clinical pathology data. For example, each test result is a sign, whereas a collection of test results (e.g., hyperkalemia, hyponatremia, azotemia, isosthenuria) is a pattern. Patterns may be suggestive of a specific disease (e.g., hypoadrenocorticism) or diseases. Just as it is impossible to conclude the pattern of results without an understanding of the individual test results (signs) with clinical pathology data, it is impossible to recognize a radiographic pattern of lung pathology without an understanding of the signs that make up the pattern. Radiographic assessment of pulmonary disease is less intimidating when you clearly define the signs detected rather than just concluding patterns.

Normal Lungs

The first consideration when evaluating radiographs for pulmonary disease is whether the lungs are normal. In general, this is determined by the opacity of the lungs and the question, "Are the lungs too white?" In a normal lung, the only soft-tissue opacities that can be detected are those of the pulmonary blood vessels. Increased soft-tissue opacity in the lung can be due to multiple factors, including obesity, underinflation, radiographic technique, and/or disease. An increase in softtissue opacity should be routinely described only if it is thought to be due to disease but not due to technical factors or age-related changes. Certain signs aid in assessing whether the radiograph was made during inhalation or exhalation, including the amount of contact between the heart and the diaphragm and the level at which the diaphragm intersects the vertebral column (T9-10 during exhalation; T11-13 during inhalation). Additionally, normal aging changes should be noted but not attributed to substantial pulmonary disease. These include ossifying pulmonary metaplasia and mineralization of the bronchi. The radiographic signs of ossifying pulmonary metaplasia are generalized, multifocal, tiny, circular, mineral opacities that are not associated with the pulmonary blood vessels. Mineralization of the bronchi is characterized by sharply margined mineral opacities that create thin, welldefined lines and rings. Increased opacity in the lungs must also be differentiated from increased opacity in the pleural space, mediastinum, and body wall.

Location

Location is the most important radiographic sign in determining the differential diagnosis. The best localization that we can probably achieve radiographically is similar to that achieved by the gross pathologist. Therefore, it is logical to use the same gross anatomic categorizations used by pathologists.¹² For example, gross pathologists rely on the location and distribution of the lesion as the primary factors in determining an appro-





priate list of diagnostic differentials. They then modify the description with other signs (e.g., suppurative, fibrinous) to further refine the list of possible causes. The same principle can be applied to radiographic interpretation. Lesions are categorized into five basic patterns of distribution: cranioventral, caudodorsal, diffuse, focal, multifocal.¹² In dogs and cats, there are two lungs that are divided into seven lobes. The lungs can be arbitrarily divided into two lung fields (cranioventral and caudodorsal) by drawing a line as illustrated in Figure 2. On a lateral radiograph, the cranioventral lung field is cranial to and superimposed on the cardiac silhouette; on dorsoventral or ventrodorsal radiographs, it encompasses the cranial two thirds of the thorax. In dogs and cats, the cranioventral lung field generally



Figure 4—Lateral (A) and ventrodorsal (B) radiographs of a dog with a severe increased opacity in the ventral part of the cranioventral lung field that obscures the pulmonary blood vessels and creates airbronchograms (alveolar pattern). The entire lung field does not need to be affected for the distribution to be classified as cranioventral.

Figure 4B—Ventrodorsal

consists of the left and right cranial and right middle lung lobes; the caudodorsal lung field consists of the left and right caudal lung lobes. However, there is some overlap of lung lobes and lung fields.

As illustrated in Table 1, the differential diagnosis is more concise when using location as the primary radiographic sign, rather than lung pattern. For example, an increased opacity in the **cranioventral** lung field is most often associated with bronchopneumonia, traumatic hemorrhage, or neoplasia whether the pattern is intersti-

	Traditional Patterns			Location				
Differential Diagnosis	Alveolar	Bronchial	Interstitial	Cranioventral	Caudodorsal	Diffuse	Multifocal	Focal
Pneumonia	Х	Х	Х	Х				
Hemorrhage	Х		Х	Х	Х	Х		
Infarction	Х		Х					Х
Primary neoplasia	Х	Х	Х				Х	Х
Metastatic neoplasia			Х			Х	Х	Х
Atelectasis	Х		Х	Х	Х	Х		
Edema, cardiogenic	Х	Х	Х		Х	Х		
Edema, noncardiogenic	Х	Х	Х		Х	Х		
Fibrosis		Х	Х			Х		
Abscess			Х				Х	Х
Granuloma			Х				Х	Х
Bronchitis		Х	Х			Х		

Table 1. Comparison of Traditional Lung Patterns and Location for Determining a Differential Diagnosis



Figure 5A—Severe bronchial pattern



Figure 5B—Miliary nodular pattern

Figure 5—Examples of a severe bronchial pattern (A) and a miliary nodular pattern (B). Differentiating between thick lines and rings, fluid-filled bronchi, and miliary nodules can be difficult.

tial, bronchial, or alveolar. Prioritization of these differentials can be further refined by assessing whether the distribution is unilateral or bilateral and noting whether one or more lobes is affected. For example, neoplasia, trauma, and lung lobe torsions are usually unilateral and affect only one lung lobe. Alternatively, increased opacity in the **caudodorsal** lung field is attributed to pulmonary edema (either cardiogenic or noncardiogenic), hemorrhage, neoplasia, or fibrosis regardless of the pattern seen (Figure 3). The differential diagnosis for noncardiogenic pulmonary edema is extensive and includes neurogenic edema, electrocution, asphyxiation, inhaled toxin, disseminated intravascular coagulopathy, vasculitis, and acute respiratory distress syndrome. **Diffuse** pulmonary disease is often simply an extension of the caudodorsally distributed disease; however, embolic pneumonia, thromboembolism, and pulmonary eosinophilic infiltrates should also be considered. The diagnostic differentials for **focal** and **multifocal** nodules are the same as those used for any mass lesion: hematoma, granuloma, abscess, and neoplasia. A prioritized differential diagnosis will vary with signalment and medical history. For example, pulmonary abscess is more common in large animal species, whereas multifocal nodules would most likely be neoplasia in a geriatric dog. Additionally, if the nodules are cavitary (i.e., contain gas and fluid), neoplasia, pneumohematoceles, and abscess are considered.

Severity of the Opacity

In general, the more opaque (white) the lungs are, the more severe the disease. For unstructured opacities, an increase in opacity that partially silhouettes with the pulmonary blood vessels, making their margins less clear, represents a lesion that is less severe than when the opacity totally obscures the pulmonary blood vessels, heart, or diaphragm (positive silhouette sign). An airbronchogram sign, defined as an air-filled bronchus



Figure 6—Flow chart illustrating the radiographic sign approach to assessing pulmonary disease, with emphasis on location.

surrounded by a soft-tissue opacity that totally silhouettes with the pulmonary blood vessels, indicates severe disease because the entire air space is filled with fluid and/or cells (Figure 4). A lobar sign represents a clear distinction of a nonaerated lung lobe adjacent to an aerated lung lobe. It is also a sign of more severe disease because an entire lung lobe is affected. These distinctions are similar to previous descriptions of interstitial and alveolar lung patterns; however, they are now used as modifiers of severity and not conclusions of histologic location.

Lines and Rings

An opacity that creates parallel lines and rings seems to be problematic. This sign was first introduced to explain the lung opacity noted in cats with bronchial disease and, therefore, has always been associated with airway disease.¹ However, lymphatics, blood vessels, and interstitial tissue also follow the airways, and disease in any one of these structures could result in a pattern of opacity that looks like lines and rings. Therefore, it would be incorrect to make the assumption that any opacity appearing to follow the airways is associated only with the bronchi. Again, it is important to remember that microscopic lesion localization cannot be determined from a radiograph and disease of any structure that accompanies the airways could result in an opacity of lines and rings. It is also confusing when the disease actually does involve the airways and the bronchi are

filled with fluid. This will result in the radiographic sign of small, circular, soft-tissue nodules. That sign alone would result in a differential diagnosis that includes metastatic neoplasia, embolic pneumonia, and fungal disease. It can be very difficult to differentiate fluid- or cell-filled bronchi from miliary nodules (Figure 5).

Size

Lung size is an important consideration when evaluating lung disease. If the lung is decreased in size (atelectatic or collapsed), there will be an increased opacity that might not be due to an infiltrate. Radiographic signs that support decreased lung size are a mediastinal shift (the heart displaces toward the small lung), crowding of the ribs, and cranial displacement of the diaphragm. These signs occur because of the negative pressure in the thorax; therefore, when the lung decreases in size, some other structure must move into its place. Lung lobes with an abnormal opacity that are decreased in size represent atelectasis, whereas abnormal lung lobes that are normal or increased in size represent consolidation. This is an important distinction because consolidation always implies pulmonary disease, whereas atelectasis might be due to recumbency, sedation, or disease. Additionally, the presence of atelectasis might mask clinically important pulmonary disease. For example, when evaluating radiographs obtained on animals under general anesthesia, small nodules (metastases) might not be detected if they are within atelectatic lung lobes.



CLINICAL APPLICATIONS

The importance of radiographic signs is illustrated further by listing diseases and their radiographic and clinical signs. Rather than focusing on radiographic pulmonary patterns, the focus is on the patterns of clinical and radiographic signs associated with those diseases. Listed below are the most common radiographic signs associated with diseases commonly encountered in veterinary medicine. A flow chart illustrating the radiographic sign approach and emphasizing location in assessing pulmonary disease is shown (Figure 6). Although this approach is simplified, it is important to remember that the signs represent trends in disease patterns and that the ability to detect the radiographic signs and determine the value of those signs in the context of the patient is challenging and varies with experience.

Pneumonia

Pathologists recognize three patterns of pneumonia: bronchopneumonia, lobar pneumonia, and interstitial pneumonia. Bronchopneumonia and lobar pneumonia are closely related in pathogenesis and the distinction between them is often arbitrary based on whether nearly the entire lung lobe is involved. Interstitial pneumonias are a result of patchy to diffuse damage to the alveolar septa. Pathologists recognize that interstitial pneumonia is often worse in the caudodorsal lung field.¹² The most common radiographic sign for bronchopneumonia or lobar pneumonia is an increase in soft-tissue opacity in the cranioventral lung field. This opacity may partially or totally silhouette with the pulmonary blood vessels. Airbronchograms, a lobar sign, and/or lines and rings might be present but indicate severity. Aspiration pneumonia is a special category of bronchopneumonia; however, the radiographic signs are the same. The radiographic sign of interstitial pneumonia is increased soft-tissue opacity in the caudodorsal lung field. In large animal species, the most frequent cause of interstitial pneumonia is infectious agents, whereas in small animal species, interstitial pneumonia is relatively rare.

Pulmonary Edema: Cardiogenic Versus Noncardiogenic

The radiographic sign of pulmonary edema is an increased opacity in the caudodorsal lung field or diffuse opacity if severe. In cardiogenic pulmonary edema, an enlarged heart and enlargement of the pulmonary veins may also be detected. Again, the opacity in the lung may partially or totally silhouette with the pulmonary blood vessels, which will give an indication of the severity of the problem. Cats present a unique situation because radiographically detectable cardiomegaly may not be present and cardiogenic pulmonary edema may occur in any lung field. Therefore, in cats, heart failure should be considered when there is abnormal pulmonary opacity in any location.

In patients with noncardiogenic pulmonary edema (e.g., disseminated intravascular coagulation, acute respiratory distress syndrome, inhaled toxin, neurogenic edema, fluid overload), there will be an increase in softtissue opacity in the caudodorsal lung field. The size of the heart is usually normal.

Neoplasia

The radiographic signs of pulmonary cancer are variable. Classically metastatic or primary lung neoplasia presents with multifocal or focal nodules. Primary lung neoplasia most frequently has the radiographic signs of a single, large soft-tissue nodule or mixed soft-tissue and mineral opacity. The nodule could be cavitary. Metastatic neoplasia can present as either a solitary nodule or multiple nodules of various sizes with sharply or ill-defined margins. Additionally, metastatic neoplasia may present as a diffuse amorphous opacity or as lines and rings. Lymph node or bone involvement might also be detected.

Bronchitis

Patients exhibiting clinical signs of bronchitis often have clinically normal thoracic radiographs because the problem is bronchial irritation, which cannot be detected radiographically. In these cases, the purpose of radiography is to exclude other potential causes for cough (e.g., pneumonia, pulmonary edema, neoplasia). In some cases, however, diffuse lines and rings may be noted. This sign is not specific for bronchial disease, but in a patient with the appropriate signalment, history, and clinical signs, it supports the diagnosis. If bronchial inflammation is severe and mucus or debris obstructs the bronchi, a lobar sign and a small lung lobe may be detected. If air trapping is occurring, the diaphragm might appear flattened and the lungs hyperlucent.

Fungal Diseases

The radiographic signs of blastomycoses and many other fungal diseases can vary from diffuse amorphous opacity to multifocal miliary or large patchy nodules; radiographs also might be normal. Tracheobronchial lymphadenopathy may be present and is seen as an increased, ill-defined opacity in the perihilar region that causes ventral displacement of the caudal part of the trachea. In addition to the radiographic signs, animals exhibit clinical signs suggestive of infectious disease. Fungal disease should be considered for any abnormally increased opacity in the lung of a dog in an endemic area.

Heartworm

The radiographic signs of heartworm disease vary with the severity and duration of the infection but can include enlarged, tortuous, truncated pulmonary arteries, dilation of the main pulmonary artery, right heart enlargement, or increased soft-tissue opacity in the caudodorsal lung field or multifocally in the lung. However, the lung opacity generally is not detected unless the pulmonary arteries are concurrently enlarged. Radiographs can be normal when the infection is new or mild.

Traumatic Pulmonary Hemorrhage

The thorax is commonly evaluated in trauma patients to assess for pulmonary contusions, pleural fluid, pneumothorax, diaphragmatic hernia, and rib fractures. The radiographic signs of pulmonary contusions are ill-defined, patchy, soft-tissue opacities in various locations, and these can affect the entire lung lobe. The abnormal opacity often is unilateral (presumably worse on the side of the trauma). Traumatic pulmonary bulla can be detected and, if blood-filled, can look like soft-tissue or cavitary nodules.

CONCLUSIONS

Physician radiologists have realized that describing diffuse pulmonary disease based on histopathologic classifications is not only difficult to teach but also has poor interobserver repeatability and does not relate to the anatomy. Many now use basic radiographic signs to describe pulmonary disease. In veterinary medicine, the currently accepted lung patterns were adapted from the earlier human pulmonary literature and have never been fully assessed. Although the approach outlined here is not universally accepted, this proposed system could provide an easier and more accurate method for detecting, understanding, and communicating pulmonary disease. Although there is substantial overlap between the radiographic signs detected and the differential diagnosis, diseases can be prioritized by incorporating knowledge of clinical signs.

REFERENCES

- 1. Suter P: Interpretation of pulmonary radiographs, in Kirk RW (ed): *Current Veterinary Therapy VII Small Animal Practice*. Philadelphia, WB Saunders Co, 1980, pp 279–289.
- Watters JW: Radiographic signs of pulmonary infiltration. Compend Contin Educ Pract Vet 1(9):704–710, 1979.
- Suter PF, Lord PF: Radiographic differentiation of disseminated pulmonary parenchymal diseases in dogs and cats. *Vet Clin North Am Small Anim Pract* 4(4):687–710, 1974.
- Felson B: A new look at pattern recognition and diffuse pulmonary disease. Am J Roentgenol 133:183–189, 1979.
- 5. Farrow C: Critical thinking: The perils of patterns recognition. Can Vet J 36:57–58, 1995.
- Mathieson JR, Mayo JR, Staples CA, Muller NL: Chronic diffuse infiltrative lung disease: Comparison of diagnostic accuracy of CT and chest radiography. *Radiology* 171:111–116, 1989.
- McLoud TC, Carrington CB, Gaensler EA: Diffuse infiltrative lung disease: A new scheme for description. *Radiology* 149: 353–363, 1983.
- 8. Suter PF, Lord PF: Methods of radiographic interpretation, radiographic signs and dynamic factors in the radiographic diagnosis of thoracic disease, in Suter PF, Lord PF (eds): *Thoracic Radiography: A Text Atlas of Thoracic Diseases of the Dog and Cat.* Wettswil, Switzerland, Selbstverlag, 1984, pp 78–126.
- Myer W: Radiography review: The interstitial pattern of pulmonary disease. Vet Radiol 21(1):18–23, 1980.
- 10. Suter PF, Chan KF: Disseminated pulmonary diseases in small

animals: A radiographic approach to diagnosis. J Am Vet Radiol Soc 9:67-78, 1968.

- 11. Lord PF: Alveolar lung diseases in small animals and their radiographic diagnosis. J Small Anim Pract 17: 283-303, 1976.
- 12. Dungwort D: The respiratory system, in Jubb KVF, Kennedy PC, Palmer N (eds): *Pathology of Domestic Animals*. San Diego, Academic Press, 1992, pp 538–699.

ARTICLE #2 CE TEST

The article you have read qualifies for 1.5 contact hours of Continuing Education Credit from the Auburn University College of Veterinary Medicine. Choose the best answer to each of the following questions; then mark your answers on the postage-paid envelope inserted in Compendium.

- 1. What is the most important radiographic sign? a. opacity
 - c. size
 - d. margination b. location
- 2. Traditional lung patterns (alveolar, interstitial, bronchial) best reflect
 - a. the differential diagnosis.
 - b. a histologic lesion.
 - c. the severity of the lesion.
 - d. a gross lesion.
- 3. The first determination that must be made when evaluating lung radiographs is the
 - a. pattern of opacity.
 - b. location of the opacity.
 - c. normalcy of the opacity.
 - d. differential diagnosis.
- 4. The best level achievable with radiographic lesion localization is equivalent to
 - a. gross pathology. c. biopsy.
 - d. cytology. b. histopathology.
- 5. The presence of an alveolar lung pattern is due to
 - a. bronchopneumonia. c. neoplasia.
 - d. all of the above b. pulmonary edema.
- 6. The most likely diagnostic differential for an increased opacity in the caudodorsal lung fields that creates airbronchograms in a 6-month-old puppy that was chewing on an electrical cord is
 - a. bronchopneumonia.
 - b. cardiogenic pulmonary edema.
 - c. noncardiogenic pulmonary edema.
 - d. neoplasia.
- 7. A 7-year-old Labrador retriever with a history of vomiting has an increased opacity in the cranioventral lung field. The most likely diagnostic differential is
 - a. bronchopneumonia.
 - b. cardiogenic pulmonary edema.

- c. noncardiogenic pulmonary edema.
- d. neoplasia.

8. A 1-year-old mixed-breed dog recently adopted from the local humane society is presented with a dry cough. Radiographs reveal no substantial abnormal finding. The most likely diagnostic differential is a. bronchopneumonia. c. traumatic hemorrhage.

- b. bronchitis. d. parasitic granulomas.
- 9. The most likely diagnostic differential for an increased opacity in the caudodorsal lung field in a 13-year-old shih tzu with a history of cough and a grade 5/6 left systolic murmur is
 - a. bronchopneumonia.
 - b. cardiogenic pulmonary edema.
 - c. noncardiogenic pulmonary edema.
 - d. neoplasia.

- 10. Thoracic radiographs of a 9-year-old golden retriever reveal multiple small soft-tissue nodules. The most likely diagnostic differential is
 - a. bronchopneumonia.
 - b. cardiogenic pulmonary edema.
 - c. noncardiogenic pulmonary edema.
 - d. metastatic pulmonary neoplasia.