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Periapical Lesions: a Review of Clinical, Radiographic, and Histopathologic Features

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Context: The essential role of a general dental practitioner is recognizing the nature of the oral cavity lesions. Periapical lesions, which are observed in radiographs of patients, may have odontogenic or nonodontogenic origins. This review aimed to study differential diagnosis of common and important periapical lesions.

Evidence Acquisition: English-language literature were searched by manual and electronic search with the terms "periapical lesions", "jaw neoplasms", and "non-odontogenic lesions" in three data bases of MEDLINE, Google scholar, and SCOPUS among published studies since 2000 to 2013. All review articles, original articles, case reports, and case series were evaluated.

Results: In this study, it has been showed that many periapical lesions have not endodontic origin and not healing by root canal therapy.

Conclusions: The authors recommended to have paraclinical tests, especially vitality tests, in addition to clinical and radiographic examinations to avoid endodontic mistreatment. In suspicious cases, biopsy of lesions, referral to pathologist, and long-term fallow-up is required.

Keywords: Jaw Neoplasms; Diagnostic Errors; Odontogenic Cysts; Periapical Diseases

1. Context

The essential role of the general dental practitioner is recognizing the nature of the oral cavity lesions. Careful evaluation of every abnormal radiolucency or radiodensity observed in radiographic images of the jaws, with regard to all clinical and radiographic signs, can guide the practitioner to reach the correct diagnosis and accordingly, prevent mistreatment and patient dissatisfaction. Periapical lesions may have odontogenic or nonodontogenic origins (Table 1) (1-3). Many periapical lesions with nonodontogenic origins such as benign and malignant tumors, nonodontogenic cysts, and infections can imitate radiographic view of inflammatory odontogenic lesions (1, 2, 4). The dentists must be aware of the clinical and radiographic features of all periapical lesions to avoid unnecessary root canal treatment or retreatment. In addition, they should be aware of the indications of tissue biopsy, and if necessary, refer the patient to the specialist. The definitive diagnoses can be obtained by histopathologic evaluation and as a result, the best treatment will be performed for the patients (1).

Considering the importance and high prevalence of periapical lesions, the aim of this study was to review the common and important endodontic and nonendodontic periapical lesions, and also presenting the simple scientific guidelines in order to differentiate them.

Table 1. Jaw Lesions That Can be Observed in Periapical Area (1)

	Jaw Lesions
1	Periapical inflammatory lesions with endodontic origin
2	Nonodontogenic cysts
3	Odontogenic cysts
4	Benign jaw lesions
5	Malignant jaw lesions
6	Infectious disease
7	Granulomatous inflammation

2. Evidence Acquisition

English-language literature searched by manual and electronic search with the terms "periapical lesions" "jaw neoplasms" "non-odontogenic lesions" in three data bases of MEDLINE, Google scholar and SCOPUS among published studies since 2000 to 2013. All review articles, original articles, case reports and case series were evaluated.

3. Results

3.1. Periapical Inflammatory Lesions with Endodontic Origin

3.1.1. Periapical Granuloma and Radicular Cyst

The most common pathologic conditions in the alveo-

lar bone derived from necrotic dental pulp are periapical lesions (4). Periapical granuloma and radicular cyst can be considered as the most important lesions, which can be seen in the teeth with necrotic pulp or improper root canal therapy (5). Periapical inflammatory lesions by a secondary immune response to the presence of bacteria in the root canal as well as the distribution of their products, develop in the periapical area (6). Periapical cyst or radicular cyst is the most frequent odontogenic cyst in the jaws (7, 8). This cyst is formed by hydropic degeneration of epithelial rests of Malassez as a result of nonvital teeth stimulation in periapical region (9). The radicular cyst is a chronic inflammatory lesion with a pathologic cavity that is lined by nonkeratinized stratified squamous epithelium. The fibrous connective tissue wall of the cyst has the various degree of infiltration of inflammatory cells and small blood vessels (granulation tissue) (10). Furthermore, cholesterol crystals may be observed. They are surrounded by macrophages and multinucleated giant cells (11). If the radicular cyst is made up of granulation tissue without cavitation, it is diagnosed as periapical granuloma (12). Periapical granuloma contains infiltration of inflammatory cells such as polymorphonuclear leukocytes (PMN), lymphocytes, macrophages and plasma cells, which are supported by granulation tissue (13). Differentiation between periapical cyst and granuloma has a little importance in treatment managing and histopathologic evaluation is not usually necessary (14). These lesions are commonly asymptotic unless acute inflammatory reactions cause initiating symptoms like pain, swelling, fever, and lymphadenopathy (14). In radiographic feature, usually a well-defined or ill-defend circular radiolucency, which has surrounded dental root apex, is seen (10). Widening of periodontal ligament (PDL) in apical part of the root is usually the specific characteristic of inflammatory lesions. In some cases, loss of lamina dura and root resorption can be seen (14, 15). The treatment of inflammatory periapical lesions is extraction, root canal therapy, apical surgery, or in some cases, the combination of these (10, 14, 16).

3.1.2. Condensing Osteitis or Focal Chronic Sclerosing Osteomyelitis

Condensing osteitis or focal chronic sclerosing osteomyelitis is the focal lesion in periapical area of the teeth with necrotic or inflamed pulps, extended caries, and restorations. Furthermore, this lesion may be seen in the teeth with inappropriate root canal therapy and the teeth under occlusal trauma (17). This lesion has a higher prevalence in the mandible than the maxilla, and is most frequently located in molars areas (18). In radiographic feature, this lesion appears as a local homogeneous radiodensity in root apex area of the teeth with PDL widening. This lesion does not have radiolucent margin (14, 19). The histopathologic features show sclerosis and remodeling of bone. If the adjacent inflammatory cells infiltrated into the sclerotic bone, necrosis often occurs (14). Treatment of the lesion is similar to other inflammatory endodontic lesions; in some cases, however, radiopacity without symptoms is observed after conventional treatment. In these cases, retreatment is not required (14).

3.1.3. Scar Tissue

Another type of chronic periapical lesion is scar tissue. This lesion is the reparative response, which is characterized by the formation of dense collagen fibers instead of the mature bone (5).

Nonhealing radiolucencies in periapical areas of the teeth with favorable root canal therapy and without signs or symptoms may be due to the healing with fibrous tissue. In these cases, retreatment is not required (16).

3.2. Nonodontogenic Cysts

3.2.1. Nasopalatine Duct Cyst

Nasopalatine duct cyst is the most common developmental nonodontogenic cyst of oral cavity, which accounts for 1.3% to 4.2% of nonodontogenic cyst (14, 20). Most of the cases are asymptomatic, but sometimes show pain, swelling of the anterior palate, response to palpation of buccal and palatal structures, and pus drainage. Histopathologic evaluations show the cystic lesion, which is lined by ciliated stratified squamous epithelium with fibrous connective tissue wall, and various degrees of inflammatory cells (14, 21). In radiographic view, well-defined radiolucency can be usually seen in the maxillary midline or between the apexes of central incisors roots. The root resorption can also occurred in some cases (22). This cyst can be misdiagnose as an inflammatory periapical lesion when radiographs show a superimposition of the incisor canal or foramen over the apex of maxillary central incisors (21). In contrast to endodontic lesions, the teeth adjacent to these lesions are vital (23). Nasopalatine duct cysts are treated by surgical enucleation (14, 21).

3.2.2. Simple Bone Cyst

Simple bone cyst or traumatic bone cyst is the empty or fluid contained benign cavity in the jaw bone, which lacks epithelial cover. The histopathologic features show that the walls of the defect is lined by a thin band of fibrous connective tissue or thicken myxofibromatous proliferation, which often has trabeculae of reactive bone (14). This lesion can be rarely seen as a well or ill-defined radiolucency in periapical area. If this lesion has involved several teeth, one of the helpful characteristics in diagnosis is observation of scalloped prominence among the dental roots (14). In some cases, this lesion is similar to chronic periapical inflammatory disease (24). The involved teeth are usually vital and without root resorption (1). Exploratory surgery is necessary for diagnosis and is usually sufficient therapy (14).

3.3. Odontogenic Cysts

3.3.1. Odontogenin Keratocyst

Odontogenin keratocyst (OKC) is the developmental odontogenic cyst, and arise from cells rests of dental lamina (14). In microscopic features, the lining of cystic lesion consists of a relatively uniform layer of parakeratinized stratified squamous epithelium with six-cell to ten-cell thickness without rete ridge formation and with corrugated surface. The basal layer of cuboidal to columnar cells with hyperchromatic and palisaded nuclei is observed. The connective tissue wall may be containing epithelial islands or daughter cyst, and some cases may have acute or chronic inflammation (25).

The OKC affects mainly the posterior area of the mandible. This lesion is usually asymptomatic, but some present with pain, swelling, and pus drainage (26). Radiographic features consist of a unilocular or multilocular well-defined radiolucency with or without root resorption (27). This lesion has an aggressive behavior and high rates of recurrence (26).

According to performed studies, the most important nonendodontic periapical lesion is odontogenin keratocyst (28, 29). It comprises about 0.7% of all periapical cysts (3). In contrast to endodontic lesion, the conservative treatment of OKC is enucleation and curettage. Due to high rates of recurrence, the patient with this lesion should be followed up after five years of treatment (25, 28).

3.3.2. Lateral Periodontal Cyst

Lateral periodontal cyst (LPC) is one of the developmental odontogenic cysts with dental lamina rests origin. Histopathologic evaluation shows that the cystic cavity is lined by thin stratified squamous epithelium and in some area, by focal nodular thickening (14).

Most of the lesions are asymptomatic. This lesion can be misdiagnosed as a lateral radicular cyst, because of the similar radiographic features including radiolucency along lateral root surface (14). In spite of this fact, lateral radicular cyst has inflammatory source and is caused by periodontal diseases or infectious diffusion of the necrotic pulp through accessory canals. Treatment of this lesion includes conservative enucleation without root canal therapy (30).

3.3.3. Calcifying Odontogenic Cyst

Calcifying odontogenic cyst (COC) or Gorlin's cyst is an unusual odontogenic lesion, which is most often asymptomatic and has similar frequency in the mandible and maxilla. Generally, 65% of these lesions are in the anterior jaw (31). In histopathologic examination, a cavity with a fibrous capsule and an odontogenic epithelium lining, with epithelium basal cells similar to ameloblasts, is seen. The characteristic feature of COC is presence of ghost cells within the epithelium. Calcification area within the ghost cells is often seen (32). In radiographic view, it seems as a unilocular or multilocular well-defined radiolucency and occasionally with diffuse radiopaque areas (33). Some cases are reported in the periapical area. The definitive diagnosis of the lesion is only based on histopathologic analysis (32). The conservative treatment is enucleation of the lesion (14).

3.4. Benign Jaw Lesions

3.4.1. Central Giant Cell Granuloma

Central giant cell granuloma (CGCG) is mostly the reactive lesion than the true neoplasm (14). This lesion is more common in anterior segments of the jaws and usually crosses through the midline. Radiographic features of these lesions include a well-defined unilocular or multilocular radiolucency (14, 34).

Based on clinical and radiographic features, these lesions have a spectrum of behavior ranging from nonaggressive to aggressive. Nonaggressive type has slow growth and low recurrence rate. Root resorption and cortical perforation is uncommon. In aggressive type, the rapid growth, high rate of recurrence, cortical bone perforation, root resorption, and tooth displacement have been observed (35, 36).

In histopathologic examination, this lesion consists of proliferating endothelial cells, fibroblasts and myofibroblasts, small blood vessels, and multinucleated giant cells in a connective tissue. Furthermore, extravasation of red blood cells and deposition of hemosiderin may be seen (35, 36).

The involved teeth of this lesion are vital. Treatment is curettage, but radical surgery may be needed for aggressive type (37). If this lesion is observed in periapical area, it can be misdiagnosed as endodontic inflammatory lesions, and as a result, root canal therapy would not be effective (14). Therefore, the lesion will grow again after treatment and lead to more bone destruction (14, 35, 36).

3.4.2. Ameloblastoma

Ameloblastoma is the second most common odontogenic tumor after odontomas, which originates from odontogenic epithelium (38). The posterior region of the mandible is the common site of ameloblastoma (14). This lesion occurs in three different types of clinicoradiologic features including conventional solid, unicystic, and peripheral. Furthermore, several histopathologic subtypes are recognized. The most common histopathologic pattern is follicular that is comprised of the islands of loosely arranged cells resembling the stellate reticulum of enamel organ which surrounding by columnar ameloblastic-like cells with reversed polarity. Plexiform type of ameloblastoma consists of long cords or sheets of odontogenic epithelium (14). Luminal unicystic ameloblastoma is confined to the luminal surface of the cyst with a lining that consists totally or partially of am-

eloblastic epithelium. There are one or more nodules of ameloblastic projects from the cystic lining into the lumen in intraluminal unicystic ameloblastoma. In mural unicystic ameloblastoma, the cyst wall consists of islands of ameloblastoma (14, 38). This lesion can be mistaken by endodontic inflammatory lesions provided that it appears surrounding the root apexes (38, 39). In early stages, the radiographic views show a well-defined unilocular radiolucency (14, 40). Ameloblastoma in this stage may radiographically mimic an endodontic periapical lesion that makes the correct diagnosis difficult (39, 41). Many studies showed that this lesion is more often asymptomatic or may cause a painless swelling of the jaw (14). However, unlike of endodontic lesions, it can be changed to multilocular radiolucency with the soap-bubble or honeycombed appearance. Furthermore, this lesion has the ability of expansion into bone, cortical perforation, teeth displacement, and root resorption of the adjacent teeth (42, 43). According to the researches, pulp sensitivity tests can be useful to discriminate ameloblastoma from inflammatory periapical lesions (39). The treatment of ameloblastoma depends on subtypes of clinicoradiologic and histopathologic features; however, most of surgeons suggested the marginal resection of at least 1.0 to 1.5 cm beyond the radiologic limits of the tumor (14).

In some cases the involved teeth in the lesions shows false-negative responses. Thus, recognizing the aggressive nature of ameloblastoma helps to detect the lesion. In general, this lesion is diagnosed based on clinical, radiological, and histopathologic features (38, 39, 43).

3.4.3. Ossifynig Fibroma

Ossifynig fibroma (OF) is a rare benign jaw neoplasm, which is constructed by connective tissue of variable cellularity with mineral component in the form of trabecular or woven bones. The posterior region of the mandible is the most common site of this lesion (44). Based on the amount of calcified material, radiographic view could be mixed radiolucent and radiopaque (45). This tumor is often asymptomatic, and in some cases lead to swelling of the cortical plate of the jaw (46). In addition to conventional type, juvenile ossifying fibroma is another type of this tumor that commonly occurs in the maxilla and bony walls of paranasal sinuses. This lesion type shows the aggressive behavior and rapid growth (44, 45).

In some cases, it can imitate endodontic lesions. In contrast to inflammatory periapical lesions, it has a spectrum of radiographic features and involves vital teeth (47). If the lesion is left untreated, the growth continues. Thus, treatment of choice is complete excision of the tumor (46).

3.4.4. Periapical Cemental Dysplasia (Cementoma)

Periapical cemental dysplasia (cementoma) is one of the most common subtypes of the jaw fibrosseous lesions that often involves the periapical region of the anterior mandible. In some patients, multiple lesions are present frequently, but solitary lesions may be also observed. This lesion is usually asymptomatic (14, 48). The histopathologic features show the cellular mesenchymal tissue and collagen fibers with small blood vessels, a mixture of woven or lamellar bones, and cementum-like particles (14). It has three stages of maturation based on radiographic features. In early stage, it has well-defined unilocular radiolucency feature rounding the root apex, and there is loss of lamina dura. In this stage, the lesion is similar to some endodontic inflammatory lesion such as dental granuloma or radicular cyst. The second stage of maturation, also known as mixed stage, can be seen as the radiopaque components within the radiolucent area. In final stage, the lesion may be totally radiopaque with radiolucent border (14, 48, 49). To differentiate these lesions from endodontic lesions, in addition to the pulpal vitality testing, radiographic follow-up and histopathologic analysis is very important and helpful (14, 49).

3.4.5. Cementoblastoma

Cementoblastoma is an uncommon benign odontogenic neoplasm of the jaw, which comprises less than 1% of odontogenic tumors. This lesion is considered as the true neoplasm of cemental origin (50). Mandible is involved more than maxilla (14). These lesions grow slowly and are usually asymptomatic, but might occasionally have mild pain. The localized expansion of cortical plates of bone is the typical feature of cementoblastoma in many of patients (51). Radiographically, cementoblastoma consists of well-defined radiopacity with a cortical border, which is confined by a radiolucent margin. The outline of the involved root would be totally damaged due to root resorption and the tumor fusion to the teeth (14, 52). In general, in early stage of this lesion, most of the affected teeth respond normally to the vitality tests. Due to extension of tumor into root canal in final stage, pulp necrosis can occur and they may not respond to the vitality tests. Unlike the inflammatory endodontic lesions, cementoblastoma has an unlimited growth potential and root canal therapy cannot stop tumor growth (52). The treatment of choice is total excision of the lesion with involved tooth (14).

Another similar lesion to cementoblastoma is apical hypercementosis, which could be defined by smaller size and absence of pain or jaw expansion. In addition, unlike the lesion in the condensing osteitis, the radiolucent margin is not detected (53). Some case report studies have been shown other rare benign lesions in periapical area containing myxoma, Pindborg tumor, squamous odontogenic tumor, intrabony hemangioma, lipoma, and amalgam tattoo (3, 5, 54, 55).

3.5. Malignant Jaw Lesions

Some periapical lesions of nonendodontic origin might mimic lesions of endodontic origin. Several malignant lesions are observed in periapical area such as lymphoma,

leukemia, multiple myeloma, squamous cell carcinoma, adenocarcinoma, chondrosarcoma, osteosarcoma, and metastatic lesions (1, 3, 5, 56-59). Lymphoma is a malignant neoplasm of lymphoid system, and very rarely occurs in jaws. Lack of knowledge about this lesion may lead to delay in diagnosis and poor prognosis. In most cases, diagnosis of malignant lymphoma in jaw bone is delayed and some of these cases have been diagnosed after nonhealing extraction wound (56).

Chondrosarcoma is a malignant tumor with cartilage formation by malignant mesenchymal cells. Less than 1% of all chondrosarcomas occur in the head and neck. Pain at the lesion is less severe than osteosarcoma, and less than 50% of patients with chondrosarcoma of the jaws complain of pain. it might cause nasal obstruction in cases with maxilla involvement (58).

Malignant lesions in periapical area can create a view similar to endodontic periapical lesion. In clinical and radiographic examinations, existence of dental caries, root resorption, irregular radiolucency, and localized tooth mobility without periodontal disease indicates the need for further investigation. Moreover, observation of sensation disorder, previous endodontic treatment failure, unusual pain, and swelling emphasize on the necessity of more radiographic and clinical or histopathologic evaluations (60).

Radiographic view of periapical malignant lesions might be an ill-defined radiolucency without cortical border. Sometimes, the remained bony islands in the radiolucent area can create a patchy appearance (59). Radiographic features of chondrosarcomas or osteosarcomas consist of rarefaction and focal calcification. However, lytic areas are observe in the first stages of these lesions. Metastatic lesions of breast and prostate can induce bone formation (58, 59, 61).

Furthermore, in radiographic features of malignant lesions, irregular PDL widening and loss of lamina dura would exist due the tumor invasion along the PDL. These cases can be confused with infectious periapical lesions and periodontal disease. However, endodontic treatment and treatment guidelines for periodontal disease cannot stop the growth of the lesion; the lesion continues to grow and is exacerbated symptoms (57). In addition, these lesions may invade the nerves and surrounding structures (60). In general, any unusual symptoms including bone destruction with rapid or slow growth adjacent to the vital teeth should be considered for biopsy (58).

3.6. Infection Disease

In some studies, infection disease such as actinomycosis, histoplasmosis, and aspergillosis have been observed in periapical areas (1). Actinomycosis is one of the most common periapical infections, which in many cases no improvement is achieved by usual root canal therapy. The histopathologic examination demonstrates a band of fibrous connective tissue with chronic inflammatory cells infiltration and colonies of organisms (14). In these cases, in addition to endodontic treatment, antibiotic therapy, and occasionally, apical surgery is required (62).

3.7. Granulomatous Inflammation

Granulomatous inflammation is identified by the granulation tissue found in periapical granulomas (63). Granulomatous inflammation can be observed in some cases such as foreign body reaction, fungal and mycobacterial infections, and cholesterol derivatives from cell necrosis. The histopathologic examination shows diffuse infiltrate of macrophages and multinucleated giant cells (14). The role of these lesions in failure of endodontic treatment is not understood well. However, biopsy and complete removal of the lesion is necessary (1, 63).

3.8. Diagnosis and Treatment of Periapical Lesions

At the time of observation of any periapical lesion, the first probable diagnosis is inflammatory endodontic lesion. Thus, in the first step, medical and dental history as well as intraoral examination including dental and periodontal evaluations should be done. History of any kind of pain or teeth hypersensitivity should be recorded. Most of inflammatory periapical lesions have no symptom until acute inflammatory reaction. Swellings or displacement of the adjacent teeth have been observed only in very large lesions (2). Radiographic evaluations are very important to differentiate lesions from each other. Lesions of endodontic origin do not separate from root apex by changing the view of x-ray radiation (14). In the final step, pulpal vitality tests including thermal and electrical tests can be useful for diagnosing vital from nonvital teeth. Although, the results of tests are not always definitive, the teeth with periapical inflammatory lesions most often do not respond to vitality tests. It should be noted that these tests are only helpful for distinguishing nonvital from vital pulp, but cannot identify different types of pathologic lesions. Furthermore, vitality testing in some cases such as teeth under orthodontic treatment, calcified root canal, traumatized teeth, teeth with open apexes, large amalgam restoration, and metal crown does not provide definitive responds. In these cases, more clinical and radiologic evaluation and history of dental treatment are required (2, 3). If the vitality tests results are positive, the nonendodontic origin is confirmed. In these cases, more assessment and biopsy are needed. On the other hand, endodontic origin cannot be determined with certainty by negative test result (2). If the endodontic origin is confirmed, the root canal therapy is indicated. If the patient has pain during the cavity preparation or canal instrumentation without local anesthesia, the initial diagnosis should be suspected and more evaluation might be needed (2, 3).

If the lesion size becomes larger or unchanged one year after treatment, it will probably never improve and endodontic treatment has failed (64). Gallego Romero et al. suggested the guidelines for treatment of periapical lesions.

Table 2. Guidelines of the American Association of Endodontics for periapical lesions (2)

Periapical Lesions Characteristics	Therapeutic Approach
Diameter < 5 mm	Conservative approach, short-term follow-up
Diameter of 5-10 mm with endodontic diagnosis	Conventional root canal therapy, 3 months follow-up
No healing 3 months after treatment	Consultation with oral and maxillofacial surgeon before retreatment
Diameter > 10 mm	Consultation with oral and maxillofacial surgeon and conventional root canal therapy

Table 3. Indications for Biopsy of Periapical Lesions (14, 63)

	Indications for Biopsy of Periapical Lesions
1	Lesion adjacent to the root apex of vital tooth
2	Persistent lesion or with progressively growing adjacent to the periapical of tooth with root canal treatment
3	Lesion adjacent to the root apex after proper endodontic retreatment
4	Lesion with irregular radiolucency, advanced mobility without periodontal disease
5	Lesion which separate from root apex by changing radiation aspects
6	Lesion with unusual radiographic view in the tooth without caries or with low caries
7	Persistent PA lesion with unusual symptoms such as sensation disorders
8	Persistent PA lesion or with progressively growing in the patient with history of malignancy

This guidelines are expressed in Table 2 (2). According several studies, periapical lesion with conservative endodontic treatment failure should be evaluated histopathologically. Guidelines of the American Association of Endodontics explain that histopathologic evaluation of all nonhealing periapical lesions is essential (1).

Incorrect diagnosis of periapical lesions may lead to unnecessary root canal therapy, additional costs, and patient dissatisfaction (39). According to performed studies, 12% of periapical lesions have nonendodontic origin. In these cases, biopsy and histopathologic evaluations can be helpful (65). The biopsy indications are summarized in Table 3 (14, 64).

4. Conclusions

To avoid endodontic mistreatment, the dentist should know all odontogenic and nonodontogenic lesions that may present in periapical areas. It is recommended to perform paraclinical tests especially vitality tests in addition to clinical and radiographic examinations. In suspicious cases, biopsy of the lesion, referral to the pathologist, and long-term fallow-up is required.

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Authors' Contributions

Saeedeh Khalesi: Main author and researcher; Seyed Mohammad Razavi: scientific collaboration; Sima Kiani contribute in information collection and edit.

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