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Research article

A probable primary malignant bone tumor in a pre-Columbian human humerus from Cerro Brujo, Bocas del Toro, Panamá^{*}

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ABSTRACT

We present a rare case of primary bone cancer principally affecting the right humerus of a skeleton from the pre-Columbian site of Cerro Brujo (1265-1380 CE) in Bocas del Toro, on the Caribbean coast of Panamá, excavated in the early 1970s. The humerus contains a dense, calcified sclerotic mass with associated lytic lesions localized around the midshaft of the diaphysis. Evidence of systemic inflammation and anemia, likely caused by the cancer, are visible in the form of severe porotic hyperostosis of the cranial vault and bilateral periosteal reactions in the tibiae. Differential diagnosis and future probes of the tumor are discussed. A tooth from the individual yielded a radiocarbon date 150 years later than those of the domestic occupation at the site. Given that it was the only formal burial recovered from the site, and as the individual had such a visible, painful, and rare pathology, this likely constitutes a ritual burial.

1. Introduction

Compared to other maladies, cancer in ancient humans seldom appears in the paleopathological literature, primarily due to the difficulty in identifying cancer from its often non-specific inflammatory skeletal manifestation. Most ancient skeletons afflicted with cancer display lesions of metastatic cancer, originating outside of the skeleton itself (Aufderheide and Rodríguez-Martín, 1998). Primary cancers of bone are rare in modern clinical settings, and even rarer to find in archaeological contexts (Capasso, 2005; Waldron, 2009). The handful of potential diagnoses of bone sarcomas (i.e., malignant tumors of mesenchymal origin) that have appeared in paleopathological literature refer to areas of the world where a plethora of skeletons have been recovered and analyzed, including Egypt, Europe, and Andean South America (Suzuki, 1987; Aufderheide et al., 1997; Gładykowska-Rzeczycka, 1997; Alt et al., 2002; Ortner et al., 2012). Most recently, a case of osteosarcoma was described in a nearly two million year old hominin metatarsal bone, highlighting the antiquity of this type of cancer (Odes et al., 2016).

This study reports a probable case of a primary malignant neoplasm affecting the right humerus of a skeleton recovered from the pre-Columbian site of Cerro Brujo (CA-3) in Panama. We describe in detail the macro- and microscopic appearance of the neoplasm, its radiological morphology, and through differential diagnosis consider its likely diagnosis. To our knowledge, this is the first case of probable cancer reported from a pre-Columbian site in Central America.

1.1. Archaeological background

The site of Cerro Brujo (CA-3) is located on the Aguacate Peninsula in Almirante Bay in the province of Bocas del Toro in Western Panama (see map, Fig. 1). This site consists of features belonging to a small group of dwellings, including refuse heaps with abundant marine shell and vertebrate remains. It was excavated by Olga Linares and Anthony Ranere in 1970 as part of a broader research project on the ecology and prehistory of Western Panama (Linares de Sapir, 1971; Linares and Ranere, 1980). Cerro Brujo was interpreted to be a small hamlet, where subsistence practices combined farming in cleared forest patches, with shell collection and fishing in inshore marine waters, hunting terrestrial mammals near the settlement, and capturing marine turtles and manatee along the coast (Borgogno and Linares, 1980; Linares, 1976; Linares, 1980a; Wing, 1980). The site is inferred to have had two occupations: the first about 600 CE, based on ceramic typology and chronology, and the second between 780 and 1252 CE according to four radiocarbon dates inferred from charcoal in middens (re-calibrated with IntCal 13; Linares, 1977, 1980a).

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Fig. 1. Map of Panama showing the location of the Cerro Brujo site.

The individual (burial 6H) described here was one of only two burials encountered at Cerro Brujo. The burial was situated in the largest of the five refuse middens (CA-3a). Burial 6H consisted of only a partial skeleton, which seems to have been tightly wrapped and placed face-down in the burial pit (see Fig. 2). Several clay pellets (likely the rattles inside the legs of tripod pottery vessels), two complete plain ceramic vessels, and a trumpet made of an Atlantic triton shell (Charonia variegata) were found in association with this burial (Linares, 1980b). Linares and Ranere (1980:299) inferred that it intruded into strata belonging to the second occupation phase (ca 900-1100 CE). A tooth from this individual returned a radiocarbon date of 700 \pm 30 BP (cal 1265-1300 and 1370-1380 CE [β -443714], ¹³ δ : -13.6), placing this burial slightly later than the four other reported dates at the site (all falling between 970 and 990 \pm 90 BP, calibrated with IntCal 13 at a 95.4% confidence interval to between cal 780 and 1252 CE, with an estimated ${}^{13}\delta$ value of -25). In fact, the date for burial 6H is one of the latest dates reported in the Almirante Bay (Thomas Wake, pers. comm. 2016) and aligns with radiocarbon dates from the nearby site of Sitio Drago (690-1410 CE; Wake et al., 2013).

2. Materials and methods

Analysis of the skeleton from burial 6H followed standard methods for osteological data collection laid out by Buikstra and Ubelaker (1994). Due to the absence of the os coxae, the age and sex of this individual were estimated based on dental development (Ubelaker, 1989; AlQahtani et al., 2010), and morphological cranial indicators (Acsádi and Nemeskéri, 1970), respectively. The fusion stages of the cranial sutures and the annular rings of the vertebral bodies were also used in the estimation of age (Schaefer et al., 2009).

The pathologies present in the skeleton of burial 6H were observed and described macroscopically, followed by examination of select lesions with a dissecting microscope (Leica Wild M10 Stereozoom). The inner structure of the main lesion was subsequently examined radiographically (AmRad CMP 200 Digital-Ready Radiographic Generator) and through high resolution computed tomography (GE LightSpeed VCT 64-slice) using the facilities of Centro Radiológico Metropolitano and the Radiology Department of Hospital Punta Pacífica, respectively; both are located in Panama City, Panama.

3. Results

An estimated age at death between 14 and 16 years for burial 6H was made based on light dental wear, the absence of third molars, the open nature of the cranial sutures, and the partial fusion of the cervical vertebral annular rings. Unfortunately, the epiphyses of the long bones were largely absent from the skeletal material recovered with this burial, and none of the areas of epiphyseal fusion were observable for age at death estimation. While it is possible that this individual simply lacked all four third molars congenitally, all other observable skeletal age indicators are consistent with an age at death around the time of puberty to late adolescence. Burial 6H appears feminine with regard to



Fig. 2. Excavation photo of burial 6H in situ. From Linares de Sapir (1971); reproduced with permission.



Fig. 3. Graphic representation of burial 6H's skeletal preservation.

cranial morphology (Acsádi and Nemeskéri, 1970) and the general gracile nature of the postcranial skeleton. However, due to the absence of the more reliable pelvic morphological features and given the estimated young age of the individual, the sex of this individual could not be determined with a degree of confidence.

Most of the skeletal elements belonging to burial 6H are fragmentary, but retain good cortical bone condition. While the cranium was able to be reconstructed from the fragments, many of the postcranial elements were missing large portions of the bones, which assumedly were not recovered from the field. The partial presence of the postcrania limited the reconstruction and observability of these bones, particularly in the case of the vertebrae and ribs. Furthermore, portions of the diaphyses of the left humerus and right femur were unobservable due to their being removed and destroyed in the 1980s for isotope analysis (Norr, 1991). Fig. 3 gives a graphic representation of the skeletal elements present with burial 6H.

Upon macroscopic observation, several pathological lesions were noted on the skeleton. Linear enamel hypoplasias were noted on the maxillary and mandibular anterior dentition, with a maximum of three hypoplastic episodes visible on the left maxillary canine. The teeth also show light calculus around the cementoenamel junction, lingual surface attrition of the maxillary anterior teeth (LSAMAT; noted by Irish and Turner (1987) and Smith-Guzmán (unpublished data) in other pre-Columbian populations in the central region of Panama), and one small carious lesion affecting the buccal pit of the mandibular right 2nd molar.

The cranial vault was abnormally thick with a porous cortical surface, principally affecting the superior surface of both parietal bones.

The pores were generally characterized by both macro- and micropores, being coalesced in many regions and appearing to represent a mixed reaction of both active and healed porotic hyperostosis (see Fig. 4). The cortical surfaces of the superior occipital and frontal bones, as well as the orbital roofs, all presented mild porosity. Active periosteal reactions affected the medial, posterior, and lateral aspects of both tibiae; being more prominent in the left tibia.

The diaphysis of the right humerus contained a large, endosteal, sclerotic mass characterized by highly mineralized bone associated with an enlarged diaphysis and localized lytic lesions between the proximal third and midshaft of the bone (see Fig. 5). This lesion lacked the typical unorganized woven bone characteristic of a fracture callus. The lytic lesions appearing on the anterior aspect of the enlarged midshaft are sharp-edged, having a moth-eaten appearance and associate with dense endosteal matrix, identifiable in Fig. 5 as darker, yellow-hued material protruding through the lighter cortical bone. Several large areas of cortical bone disruption appear on the anterior and medial aspects of the lesion. These large areas are characterized by whiteedged cortical borders indicative of post-mortem damage to the bone. It is possible that the lesion extended beyond the cortex of the bone, perhaps through the areas with post-mortem damage. However, if such an extension existed, it was either not noted during the excavation, or was lost due to taphonomical processes previous to excavation.

Radiographically, there is a mid-diaphyseal expansile lesion that is ill-defined with irregular dense matrix and bony destructive changes (Fig. 6). The aggressive lytic changes are more fully demonstrated on the CT scan (Fig. 7). The endosteal lesion measures approximately 4.7 cm in length and 2.0 cm in width.

4. Discussion

The potential causes of the pathological changes observed in burial 6H are considered in differential diagnosis in the paragraphs to follow. The lesion affecting the right humerus from burial 6H is characterized by both aggressive and non-aggressive radiological features (see Table 1). Therefore, considered among potential conditions causing endosteal expansile lesions (Table 2) are osteomyelitis, enchondroma, fibrous dysplasia, as well as primary bone neoplasms, the descriptions of which were consulted in both clinical and paleopathological literature. Enchondroma favors the small tubular bones of the extremities, typically represented by lesions smaller than 2 cm in length (Miller, 2008); thus, if the lesion affecting the humerus of burial 6H is of cartilaginous origin, chondrosarcoma is more likely. Fibrous dysplasia is also not likely in this case due to its typical well-defined, lytic features, and its tendency to favor bones other than the humerus (Unni and Inwards, 2010). The primary bone neoplasms and osteomyelitis appear more likely, and are considered further in the paragraphs that follow.

4.1. Primary malignant bone tumors

The two most common primary malignant bone tumors in children are osteosarcoma and Ewing sarcoma. Chondrosarcoma is the second most common primary malignant bone tumor overall, but is uncommonly seen in childhood (Kaste, 2011; Mertens et al., 2015). Osteosarcoma and Ewing sarcoma arise from mesenchymal stem cells that likely remain from early embryologic development (Lin et al., 2011; Mutsaers and Walkley, 2014). The combination of lytic lesions associated with an osteoblastic mass, coupled with the appearance of dense, mineralized tissue originating from within the diaphysis of the bone and expanding outwards at a perpendicular angle is consistent with the appearance of a primary malignant bone neoplasm (Aisen et al., 1986; Murphey et al., 1997). Differentiation between these three sarcoma types in clinical settings is generally based on the age of the patient,



Fig. 4. Superior view of the cranium of burial 6H showing severe porotic hyperostosis with notable expansion of the diplöe.

appearance of the tumor, and affected area of the body. However, for definitive diagnosis, tissue sampling for microscopic evaluation, and potentially molecular probe investigations, is the current state of the art.

Osteosarcoma, the most common type of primary malignant bone tumor in children, occurs mostly in adolescents and young adults in the second decade of life, and affects males slightly more often (58%) than females (Unni and Inwards, 2010). This tumor favors the distal femur, proximal tibia, and proximal humerus, but can affect other long bones and rarely the skull. Osteosarcomas can cause a lytic, sclerotic, or mixed reaction of the bone affected, taking on a characteristic "sunburst" appearance of spiculated bone extending perpendicular to the cortex, a "cauliflower" appearance of lobulated sclerotic bone, or a "moth-eaten" appearance of permeated bone. Often, the "Codman's Triangle" formation of reactive bone lifting away from the tumor is seen (Murphey et al., 1997; Kundu, 2014). Unlike the lesion seen in burial 6H, osteosarcomas tend to affect the metaphyses of the long bones. However, a modern study of 1952 cases of osteosarcomas (excluding parosteal tumors) reported by the Mayo Clinic, the tumor was located in the midshaft of the humerus in 1.2% of all cases, and in 12.4% of all cases located in the humerus (Unni and Inwards, 2010). Occasionally,

these diaphyseal lesions have a more benign appearance, some appearing to have arisen from pre-existing benign lesions (Haworth et al., 1981).

Ewing sarcoma, the second most common primary bone tumor in childhood and adolescence, is rarely seen in adults. This tumor does not produce matrix, and, therefore, is able to permeate through intertrabecular and intracortical spaces (Ortner, 2003). Its appearance is generally lytic, involving a large segment of the diaphysis of the long bone or the pelvis and presenting an "onion skin" layered periosteal reaction with Haversian canal invasion (Granowetter and West, 2012). Thus, Ewing sarcoma tends to have a more destructive appearance than the lesion seen in the humerus of burial 6H; however, the position of the tumor in this case at approximately midshaft aligns most with Ewing sarcoma.

Chondrosarcoma, the second most common primary bone tumor, occurs primarily in individuals of adult age and rarely in adolescents, and affects males more commonly than females (Jaffe et al., 2010). This tumor appears most commonly in individuals in their fourth and fifth decades of life (Greenspan et al., 2007). They frequently affect the proximal and distal femur, proximal humerus, ribs, and pelvis, and occur uncommonly in other skeletal elements. In its mature form, the



Fig. 5. Anterior, medial, posterior, and lateral views (left to right, respectively) of the right humerus of burial 6H showing lesion near midshaft. Photos taken by Edwin Dominguez.

tumor becomes mineralized, appearing more organized, having a more nodular characteristic shape than osteosarcomas, and causing endosteal scalloping of the cortex (Ortner 2003; Jaffe et al., 2010). That the endosteal lesion affecting the humerus from burial 6H represents a chondrosarcoma appears unlikely due to inconsistencies in typical demographics, location, and morphology of this tumor.

4.2. Osteomyelitis

Osteomyelitis is an inflammatory reaction of bone which originates in the medullary cavity (Lew and Waldvogel, 2004). This process can be caused by a variety of factors, including trauma and focal or systemic infection, but is generally a result of the introduction of a pyogenic bacteria into the bone itself. Osteomyelitis favors long bones, particularly the epiphyseal regions of rapid blood flow, with the epiphyses of the femur and tibia affected in 80% of all cases. Due to the frequent involvement of pyogenic bacteria, cloacae for the drainage of pus is a key feature of osteomyelitis (Pinhasi and Mays, 2008). Children up to age 15 account for 80% of all cases. Morphological changes to the bone include surface irregularities, leading to an irregular bone architecture even after healing. The lesion present in the humerus of burial 6H lacks the surface irregularities, cloacae, and other characteristics of osteomyelitis, and contains highly mineralized bone spicules uncharacteristic of this inflammatory process.

4.3. Synthesis and cultural implications

Through differential diagnosis and upon comparison with other known cases of neoplasms on dry bone, the lesion affecting the humerus of burial 6H aligns most with the appearance of an osteosarcoma; however, its location on the diaphysis of the bone is uncommon for this type of tumor. Nevertheless, Ewing sarcoma, which does commonly affect this location, would be expected to have more lytic features visible radiographically. Furthermore, the severe lesions of anemia and inflammation visible in other areas of the skeleton suggest that this individual was afflicted by some type of physiological stressor for some time. The linear enamel hypoplasias present in the teeth of this individual and the periosteal reaction visible in the tibiae could be the result of an unrelated childhood disease or malnutrition. However, the porotic hyperostosis observed on this individual is more severe in regard to diploic expansion than that of any of the cases observed on any ancient Panamanian human remains to date, and thus, likely



cancers affecting children and adolescents are thought to be associated with rapid growth along the metaphyses of the bone. In the case of

having appeared during early growth and migrated to the midshaft of the humerus as the bone grew. Based on clinical observations of patients with primary bone tumors, the individual recovered from burial 6H at Cerro Brujo would likely have experienced intermittent pain in the right arm as the tumor slowly grew and expanded through the cortex of the humerus (Widhe and Widhe, 2000). There would have been an associated soft tissue mass, creating a swollen appearance of the right upper arm. Since this type of bone tumor has never before been recorded among the ancient populations that inhabited the Isthmo-Columbian area, it is doubtful that the population to which this individual belonged had observed this type of pathology previously.

burial 6H, this rapid growth could explain the presence of the tumor.

misdiagnose rare expressions of tumors from archaeological contexts not commonly seen in clinical settings. Further, due to differential preservation of sclerotic and lytic lesions, greater mineralization of some rare bone tumor expressions may skew the probability in favor of encountering these lesions in geographic areas prone to high taphonomical degradation of osseous tissue. Continued differential diagnosis of the lesion in the individual from burial 6H is ongoing through genetic sequencing, whereby mutations within the tumor tissue may serve as a biological fingerprint specific to each type of cancer. Although several cancers have shown evidence of infectious causes, primary bone

We cannot know with a degree of certainty the ancestral relationship of the population inhabiting Bocas del Toro 700 years ago to a specific surviving indigenous people of Panama. However, several interdisciplinary studies have found evidence suggesting that the Ngäbe (formerly subsumed under the larger umbrella term "Guaymí") have a deep and continued history of occupation in the Bocas del Toro province. After Spanish contact and until the present day, their cultural epicenter has comprised the eastern sector of Bocas del Toro, eastwards of the Valiente Peninsula, and the Pacific foothills of the opposite (Chiriqui) watershed (Linares de Sapir, 1971; Young, 1971; Linares and Ranere, 1980; Barrantes et al., 1990; Kolman et al., 1995; Constenla Umaña, 2012; Cooke, 2016). Thus, the Ngäbe of today that still keep to their traditional practices and beliefs provide clues as to the possible medical treatment and life history of the adolescent from burial 6H at Cerro Brujo.

The Ngäbe believe that sickness is caused by a disruption of the balance between the natural and supernatural worlds, in which a malevolent spirit enters the body while the afflicted is dreaming to steal the soul (Torres de Araúz, 1980; Guionneau de Sinclair, 1990). Individuals with serious illnesses are taken to a shaman (called *Sukia* in the Ngäbere language), who acts as an intermediary between the two worlds, communicating with the spirit and attempting to ensnare it. It is likely that a *Sukia* would have tried to heal the young person buried at Cerro Brujo through herbal remedies, perhaps including alkaloid-containing *Hoffmannia longipetiolata*, a plant used currently in Ngäbe communities for its analgesic properties (Huang and Baker, 2001).

Whatever the medical treatment, this individual did not overcome the illness, and died about 1300 CE shortly after reaching puberty, by which time the Cerro Brujo settlement had been abandoned. Where this individual grew up we cannot say. Archaeological surveys undertaken in this part of the coast have been irregular, and are unlikely to have identified all pre-Columbian settlements in the vicinity. The regional population may have gravitated toward Sitio Drago on the western side of Isla Colón where a village that covered 17 ha grew up after about 600 CE, and was occupied until at least 1410 CE (Wake et al., 2013), and was likely one of the trading ports described at first contact by Fernando Colón (Wake, pers. comm. 2017).

The intrusive burial of the individual in burial 6H in an abandoned settlement may reflect ancestral ties with Cerro Brujo. Other known

Fig. 6. Anterior (left) and lateral (right) view radiographs of the right humerus of burial 6H showing lesion near midshaft.

represents a unique metabolic condition probably related to the neoplasm in the humerus. If indeed the tumor was responsible for this physiological stress over many years, its shift away from the metaphysis with normal bone growth would have been plausible.

Thus, the tentative diagnosis for this tumor is osteosarcoma; however, no definitive differentiation between osteosarcoma and Ewing sarcoma can be made at this point. Nor can any of the other aforementioned conditions be ruled out entirely. A complication of attempted differential diagnosis of bone tumors on skeletal remains lies in the large range of expression of these tumors (Rosenberg et al., 1995). Paleopathologists relying on clinical descriptions of their common radiographic appearance, as in Table 2 for example, may



Fig. 7. Computed tomography (CT) of right humerus from burial 6H. Left image shows a horizontal slice through the lesion at the level of the red line shown through the sagittal slice (right). Letters provide orientation (M: medial; P: posterior; L: lateral; A: anterior; T: proximal; B: distal). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1

Radiological features of nonaggressive versus aggressive/undetermined bone lesions (based on Dumitriu et al., 2014).

	Nonaggressive	Aggressive/Undetermined	САЗ-6Н
Type of lysis	Geographic	Moth-eaten/permeative	Moth-eaten
Margins	Well-defined	Ill-defined	Ill-defined
Zone of transition to normal bone	Narrow	Wide	Narrow (sclerotic)
Bone contour	Expansion from slow growth	Destruction	Expansion, with areas of destruction
Periosteal reaction	Smooth, uninterrupted	Aggressive types (sunburst, hair-on-end, linear interrupted,	Smooth
		Codman's triangle)	
Soft-tissue mass	Absent	Present	Unknown

mortuary sites in Bocas del Toro include primary extended burials in coral-lined graves and secondary burials within urns, with few to no associated grave goods (Wake, 2014; Stirling and Stirling, 1964). In contrast, this individual was buried with two whole pottery vessels and a shell trumpet, of the kind that continues to be used in important Ngäbe traditional activities like the balsería festival (Young, 1976; Torres de Araúz, 1980). These were things that individuals might need in their journey to the afterlife (Alphonse, 1956). Rather than being cast out of society as a cursed individual, or discarded *carelessly* in the trash as a diseased individual (Linares, 1980b:139), this young person seems to have been buried with care alongside ritually significant items at a site connected with their ancestors. Ancestor veneration was widely practiced among the ancient inhabitants of the isthmus, as implied by the keeping of crania and other body parts for use in ritual activities, the re-use of descent group tombs for subsequent burials, and the burial of important individuals with isolated 'heirloom' human skeletal elements (Cooke et al., 1998; Wake, 2014). Therefore, it is reasonable to propose it likely that the remains of the adolescent were carefully laid in burial 6H in a village once occupied by her ancestors owing to cultural group beliefs about the relationship between disease, death, and the spirits of the deceased.

5. Conclusions

Based on the gross and radiographic appearance of the lesion on the right humerus of burial 6H, a retrospective diagnosis of malignant bone sarcoma was made, likely representing either osteosarcoma or Ewing sarcoma. Following modern clinical characteristics of these types of tumors, the most likely diagnosis is osteosarcoma; however, there are some discrepancies that lead to uncertainty in the diagnosis. Future diagnostic probes seeking a more narrow diagnosis of the type of sarcoma affecting burial 6H will include assessment of ancient DNA for mutations.

	Demography	Bones favored	Location	Gross pathology	Radiological features
Osteomyelitis Enchondroma	All Children to young adults; predilection toward males	Long bones, vertebrae, and pelvis Tubular hand and foot bones	Epiphyses Diaphyses	Surface irregularities, involucrum, cloacae Small lesion, mixed lytic-sclerotic	Sclerosis around lytic center Endosteal scalloping, calcifications
Fibrous dysplasia	Adolescents and young adults; medilection toward females	Skull, ribs, pelvis, femur, and tibia	Diaphyses and proximal metanhyses	Large lytic lesion (or multiple lesions), with possible associated vallow viomentation	Well-defined zones of rarefaction, often surrounded by seleratic bone
Osteosarcoma	Adolescents and young adults; predilection toward males	Distal femur, proximal tibia, and proximal humerus	Metaphyses	Large lesion, aggressive, mixed lytic-sclerotic	"Cloud-like" matrix; "Sunburst," "cauliflower," or "moth-eaten:" Codman's triangle
Chondrosarcoma	Adults 40–60 years; predilection toward females	Proximal and distal femur, proximal humerus, ribs, and pelvis	Metaphyses	Large lesion with discrete calcifications; either thickened (low-grade) or thinned (high-grade) cortex	Organized, nodular, with endosteal scalloping
Ewing sarcoma	Children and adolescents	Long bones and pelvis	Diaphyses	Lytic, involving large section	"Onion skin" layered periosteal reaction

Table 2

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijpp.2017.05.005.

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