Eosinophilic mediastinitis, myositis, pleuritis, and pneumonia of cattle associated with migration of first-instar larvae of Hypoderma Zineatum


Abstract. Migrating first-instar larvae of Hypoderma Zineatum are a frequent cause of focal inflammatory lesions in connective tissues of the mediastinum, parietal and visceral pleura, peritoneum, lungs, diaphragm, and other loci. The lesions are characterized grossly by foci of yellowish or greenish gelatinous edema and microscopically by infiltration of the edematous tissue by a dense array of eosinophils. Lesions were recognized during a period of several weeks in late spring; the timing was attributable to events in the life cycle of the fly. The larvae, which were small (≈ 1 x 4.5 mm), transparent, and unobtrusive, were recovered from lesions in 12 of 20 cattle in which careful parasitologic examination was made.

The life history, pathologic effect and myiasis control programs for Hypoderma lineatum and Hypoderma bovis (Diptera: Oestridae) have recently been reviewed. General aspects of the life cycle of H. lineatum are well known. In early spring, adults emerge from pupae that developed from third-instar larvae. These larvae entered the soil during late winter, following emergence from subcutaneous warble cavities. The adult life span is 3-8 days, during which fertilization and egg production occurs. Eggs are deposited on hairs of legs and ventrum of cattle and hatch in a few days, and first-instar larvae penetrate the skin and enter the subcutis within hours. Exact routes of the extensive migration that occurs in the host are not clear, but the esophageal submucosa is generally involved. First-instar larvae remain in the esophageal submucosa for 5-6 months and ultimately reach the subcutis of the back, where they induce a warble cavity, molt twice, and remain for 5-8 weeks. Larvae emerge from the warble, fall to the ground, pupate, and initiate another cycle.

Migration is dependent upon elaboration of a collagenase by larvae, and the migratory route is largely or entirely through the collagenous stroma of various organs. Although veterinarians are quite familiar with the esophageal and cutaneous lesions of H. lineatum infections, the pathologic changes associated with other segments of their larval migration are less well known. In addition to their usual presence in the esophageal submucosa, first-instar larvae have been observed in various loci, including the subcutis of the limbs and trunk; intermuscular fascia; fascia of epineurium of nerve trunks; peritracheal, periesophageal, and parietal pleural and peritoneal connective tissues; pericardium; visceral peritoneum of spleen, liver, rumen, and intestine; diaphragm; intercostal muscles; and the perirenal connective tissue. The histopathology of esophageal lesions induced by first-instar larval migration has been described. Lesions in periesophageal, peritracheal, and pleural connective tissues have also been reported.

Economic loss resulting from Hypoderma lineatum infection includes damage to the hide and carcass (“licked” beef, butcher’s jelly), rare anaphylactic reactions, the cost of treatment, treatment accidents (esophagitis and bloating), trimming of carcass parts associated with reactions to migrating first-instar larvae, the occasional condemnation of carcasses because of these factors, and possible loss from diminished weight gain. Gadding induced by attacks of H. lineatum appears very limited, whereas that due to H. bovis is much more severe, probably owing to the behavior of adult flies while depositing eggs. Hypoderma lineatum deposits several eggs at a time, whereas H. bovis deposits one at a time, necessitating many more approaches.

In April/May of the past 15 years, we have observed characteristic lesions associated with presence of first-instar H. lineatum larvae. Periodic inquiries regarding these lesions by veterinary and lay meat inspectors prompted this report.

Materials and methods

Observations were gathered over a 15yr period by examination of specimens from a total of 32 cattle representing 12 case groups. Formalin-fixed or fresh specimens (portions...
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Parasitic larvae were specifically and critically sought in specimens from 20 animals by careful dissection and teasing of lesioned tissue examined by direct visual scrutiny, by dissection microscope, and in some instances by use of Baer-
mann funnel apparatus. Those recovered were mounted in Hoyer’s solution and examined by light microscopy. Identification was made according published accounts.10 Multiple tissue specimens were fixed in buffered formalin, embedded in paraffin, sectioned by standard methods, and stained with hematoxylin and eosin (HE).

**Results**

The most prevalent gross lesions were vaguely outlined foci or elongated areas of yellowish or greenish edema, most frequently in the loose connective tissue and adipose tissue of the dorsocaudal mediastinum, sometimes extending forward to the level of the tracheal bifurcation. Adjacent esophageal and aortic adventitia and hilar connective tissue of the lung were often similarly affected. The crura of the diaphragm frequently had greenish edematous or gelatinous infiltration in connective tissue between muscle bundles (Fig. 1). Patches and streaks of subserosal edema were less frequently observed in epicardium and diaphragmatic and costal pleura. Regional lymph nodes were often enlarged and firm and sometimes had a yellow-green cast on the cut surface. In the few opportunities available to examine abdominal structures, focal lesions were sometimes noted in the serosa of the rumen, the greater omentum, the jejunal mesentery, and the diaphragmatic peritoneum. The lesion pattern suggested convergence of larval pathways on the esophageal hiatus of the diaphragm.

In several of the lungs, there were foci of greenish edema in the pleural connective tissue. In other areas, dense, nongelatinous, greenish infiltrate expanded interlobular septa of single or multiple areas and extended deeply into the septal connective tissue of the lung (Figs. 2, 3). Most such lesions were in caudal lung lobes. Lobular parenchyma was grossly unaffected except for occasional hemorrhage, which involved interlobular septa as well. The pleural surface of many of the lungs, especially the medial surfaces of the caudal lobes, and the diaphragmatic pleura contained aggregates of well-organized 0.1- x 1.0-cm fibrous tags, the attached ends of which were usually located over interlobular septa (Fig. 4).

Larvae were found in 12 of the 20 animals in which careful parasitologic examinations were made. Often, only a single larva was found, but in 1 animal 6 were...
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Figure 9. Bovine lung with eosinophil infiltrate in interlobular and adjacent interalveolar septa and in bronchial and vascular adventitia. Mucocellular (eosinophil) exudate is in the bronchiolar lumen.

Larvae were generally associated with the greenish edematous areas and were approximately 1 mm in diameter, 4-5 mm long, virtually transparent, and very unobtrusive (Fig. 5). Most larvae were observed in the caudal mediastinal connective tissue, but some were identified in the muscular fascia and intermascular septa of crura of the diaphragm. Intact larvae were not obtained from lung lesions, but a single pair of spiracles resembling those of *H. Zineatum* were recovered from 1 lung.

**Histopathology.** The thematic response to larval migration was an inflammatory reaction centered in connective tissue and characterized by edema, an overwhelming eosinophil infiltration with minor degrees of participation by other inflammatory cells. Fibroblastic response was minimal. The eosinophil infiltrative process often involved the wall of blood vessels.

In skeletal muscle, the inflammatory reaction was most intense in epi- and perimysial connective tissue (Fig. 6). Necrosis of muscle fibers was not prevalent. Lesions involving adipose tissue were primarily in supporting connective tissue septa; necrosis of adipocytes and attendant mono- and multinuclear cell response occurred occasionally. Capsulitis, pericapsulitis, and adenitis of regional lymph nodes were characterized by intense eosinophil infiltration of those structures, by eosinophil infiltrate of cortical and medullary sinuses and paracortical lymphoid tissue, and by follicular hyperplasia. Eosinophilic vasculitis was present in numerous perinodal vessels (Fig. 7).

Pulmonic lesions largely involved the connective tissue stroma. Discrete areas of the pleura, interlobular septa, and peribronchial and vascular adventitia contained the eosinophil inflammatory response (Fig. 8). That inflammation sometimes extended from intense septal lesions to involve adjacent interalveolar septa. Bronchial and bronchiolar adventitia and the walls of many muscular branches of the pulmonary artery were infiltrated with eosinophils (Fig. 9). Minimal pools of mucus that contained a few eosinophils were occasionally present in airways. The pleural tags had a variably cellular fibrous core and were covered by hypertrophic mesothelial cells. Some tags were densely infiltrated with various proportions of eosinophils, lymphocytes, and plasma cells; others were sparsely cellular with occasional lymphocytes.

A single lesion, apparently a larval track, had a central area of degenerate eosinophils and eosinophilic debris bordered by a narrow zone of macrophages and occasional multinucleated giant cells and was surrounded by a broad peripheral zone of small lymphocytes, eosinophils, scattered fibroblasts, collagen fibrils, and vascular sprouts. The inflammatory response to viable larvae was characterized by a thin layer of eosinophils closely apposed to the larval cuticle and by marked edema and eosinophil infiltration of adjacent tissue (Fig. 10). Endothelial cell nuclei of vessels in the area were markedly swollen.

**Epidemiology.** The submissions of cases to the laboratory were notably seasonal. Specimens originating from 11 of the 12 “herds” of origin were received between April 4 and May 3. The earliest (April 4) originated in southern Oklahoma. The remainder (April 17-May 3) were from central and western Oklahoma. Larva-induced lesions were a coincidental finding during necropsy of a single animal from northwestern Arkansas on June 10. All specimens were from animals known or judged to be 1.5-2 years old.
Discussion

The observed lesions were similar to those associated with tissue migration by numerous arthropod and helminth parasites. The pulmonic lesions resembled those induced by the migrating larvae of Ascaris suum in cattle. In that instance, prior exposure to A. lumbricoides was necessary for development of the eosinophilic response. Similarly, the participation of eosinophils in the cutaneous reaction of cattle to penetrating H. lineatum larvae requires prior exposure and sensitization to H. lineatum. All the specimens examined originated from cattle > 1 year old, which had had opportunity for prior exposure.

The highly seasonal occurrence of the lesion is a reflection of the life cycle of the fly. The flies emerge from overwintered pupae and lay eggs during a brief period in the spring. Skin penetration by larvae and their migration toward the esophageal submucosa occurs in as little as 4 weeks. Thus, the larvae and the lesions they produce in the locations described occur in a defined and limited period whose calendar dates depend largely on the dates of oviposition. The eventual fate of the “aberrant” larvae is problematic. Many first-instar larvae that penetrate the skin fail to complete migration and development to emerge as a third-instar grub. Survival may range from 0% to 85%, depending on various resistance factors of the host, such as age, previous infestation, and the immunity derived therefrom. Many larvae die within the skin shortly after penetration, especially in previously infected animals that elicit a prominent cellular response to penetrating larvae. We believe that a portion of larval mortality is represented by some of the larvae that induce the lesions described.

The pulmonic lesion is unusual and is best characterized as an eosinophilic interlobular septitis with extension to produce limited interalveolar septitis and peribronchitis/vasculitis. Minimal involvement of bronchial mucosa occurs. The pulmonic lesion is usually unifocal, a distribution more compatible with response to local migration of a parasite rather than to hematogenous or aerogenous routes of exposure. Although intact larvae have not been observed within the lung lesion, the presence of spiracles and the nature of the lesion and its coexistence with mediastinal lesions that contain larvae leaves little doubt that it results from larval migration.

The relationship of pleural tags—which have been observed in many cattle year round—and migrating larvae is less certain. Nevertheless, such lesions were found in a subacute, highly cellular stage in animals with the mediastinal lesion; at other times of year, the tags are less cellular, more fibrous, and contain occasional eosinophils. These less cellular tags were interpreted as the chronic or healed phase of the acute/subacute process.

Inflammatory lesions characterized by eosinophil infiltration of mediastinal and adjacent tissues of cattle include those caused by pentastome, ascarid, and other migrating immature parasites and by eosinophilic myositis. Migrating pentastomes most commonly inhabit mesenteric lymph nodes but occasionally are in thoracic structures. In contrast to the Hypoderma-induced lesion, pentastome-induced lesions tend to be single, more discretely defined, and often caseous and mineralized. Lesions induced by migration of Ascaris lumbricoides in cattle most frequently affect the liver and lung but apparently spare the diaphragm, mediastinum, peritoneum, and pleura. Lesions resulting from A. lumbricoides migration are multiple and widespread in the lungs. Eosinophilic myositis associated with Sarcocystis spp. is clearly a lesion of musculature rather than of collagogenous connective tissues. Eosinophilic myositis (type B) involves striated muscle throughout the body. After its very early stages, granulomatous inflammation containing eosinophils is a characteristic feature of eosinophilic myositis. Other relatively common mediastinal lesions of cattle are related to traumatic reticuloperitonitis, with penetration of the diaphragm, perforation of the thoracic esophagus, and extension of cervical inflammatory lesions into the anterior mediastinum, and to lymphoid neoplasia. Mediastinal lymphadenitis accompanies a variety of inflammatory lesions involving regional structures.

Veterinarians and lay meat inspectors should be suspicious of damage produced by migrating H. lineatum on the basis of yellow or greenish gelatinous, edematous areas in the connective tissues of the peritoneum, pleura, mediastinum, esophageal and/or aortic adventitia, epi- and perimysial connective tissue of diaphragmatic crura, and focal, generally single areas of pulmonary interlobular septitis.

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References

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