Journal of the American Society of Cytopathology (2015) 4, 203–209

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.jascyto.org/

ORIGINAL ARTICLE

Clinical presentation and cytopathologic features of malignant pericardial cytology: a single institution analysis spanning a 29-year period

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Received 7 November 2014; received in revised form 21 January 2015; accepted 21 January 2015

KEYWORDS
Malignant pericardial effusion;
Serous effusion cytology;
Adenocarcinoma;
Bodily fluid;
Cancer;
Effusion;
Liquid based cytology

Introduction Pericardial effusion can be a consequence of various diseased states, including infection, autoimmune disease, renal failure, myocardial disease, and neoplasms. Although multiple case reports of malignancy-associated pericardial effusion have been published, few database analyses are available in these published reports. In this study, we retrospectively reviewed 1022 cytology cases and assessed malignancy-associated pericardial effusion.

Materials and methods We reviewed our cytology reports for pericardial effusion cases from January 1, 1983 to July 31, 2013. These cases were classified as benign, atypical, malignant, and nondiagnostic. The malignant cases were further characterized based on either immunohistochemical staining results or patients' history.

Results We identified 1022 cases and grouped them as follows: 824 benign (80.6%), 38 atypical (3.7%), 158 malignant (15.4%), and 2 unsatisfactory (0.1%). Malignant cases included 131 adenocarcinoma (82.9%), 12 lymphoma (7.9%), 6 poorly differentiated carcinoma (3.8%), 4 mesothelioma (2.5%), 2 squamous cell carcinoma (1.3%), 1 melanoma (0.6%), 1 sarcoma (0.6%), and 1 small cell carcinoma (0.6%). Of these 131 adenocarcinomas, 83 cases had clinical history and/or immunohistochemical study available for further classification, which included 44 lung, 18 breast, 7 esophagogastric adenocarcinomas, 6 adenocarcinomas of unknown primary sites, 5 ovarian, and 2 rectal adenocarcinomas. The clinical presentation, prognosis, and cytopathologic features for malignant pericardial effusions are summarized.

Conclusions In this study, 15.4% of pericardial effusion cases were caused by metastatic malignancy, with lung adenocarcinoma being the most common primary site, followed by breast and lymphoma. Relatively young patients are affected, with average age being 56 years. Prognosis is poor for patients with malignant pericardial effusion. However, targeted therapy showed improved survival.

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2213-2945/$36
http://dx.doi.org/10.1016/j.jasc.2015.01.009

Introduction

Malignant serous effusions involving pleural, peritoneal, and pericardial cavities can be seen at the advanced stage of any neoplasm. Treatment choices are limited once tumor cells are present in serous cavities, and prognosis is dismal for the vast majority of patients. Previous studies have largely focused on pleural and peritoneal malignant effusions. The clinical presentation, prognosis, pathologic findings, and diagnostic pitfalls are well studied. In addition, substantial progress has been made in unveiling the molecular mechanisms of tumors causing malignant pleural and peritoneal effusions.[1,2] Translational therapeutics have been successful in some patients using monoclonal antibodies and small molecule inhibitors.[2]

Malignant pericardial effusions are not commonly seen. Though the heart receives blood and lymphatic fluid from the entire body, it is rarely involved by malignancy except at the end-stage disease. As a consequence, the clinical features of pericardial effusion are not well defined. Although there are case reports describing rare malignancies metastasizing to the pericardial cavity, database analyses are few in number. The most recent article analyzed 128 pericardial specimens over a 6-year period and identified 31 malignant pericardial effusions.[3] Another study collected cases spanning a period of 24 years and identified 375 cases, with 65 cases of malignant pericardial effusion.[4] The sparse literature on the subject can be explained by the relatively rare occurrence of malignant pericardial effusions, and an unwillingness on behalf of clinical teams to perform pericardiocentesis. Unless patients have cardiac tamponade symptoms, there is often a fear of severe complications in obtaining diagnostic material for study.

Distinguishing benign from malignant pericardial effusion can be difficult in cytology. However, there is a paucity of published reports describing pericardial cytomorphology. DeMay, in *The Art and Science of Cytopathology*, mentions that benign pericardial effusions can contain extremely reactive mesothelial cells,[5] whereas other books tend to combine pericardial and pleural effusion together.[6,7]

In this study, we examined 1022 pericardial cytology cases from the past 29 years at the Cleveland Clinic with a focus on malignant pericardial effusions. The etiology, clinical presentation, and cytomorphologic features of malignant pericardial effusions are summarized.

Materials and methods

Institutional Review Board approval was obtained for this study. Pericardial effusion specimens collected between January 1, 1984 and July 31, 2013 were retrieved from the Anatomic Pathology CoPathPlus (Cerner Corporation, Kansan City, Mo) database at the Cleveland Clinic. A total of 1022 cases were identified. Older cases were prepared using the cytospin method and slides were Papanicolaou-stained. From 1984 to approximately 1995, the pericardial effusions specimens were evaluated using the cytospin method. From 1995 to current day, cases were prepared with the ThinPrep (Hologic, Marlborough, Mass) method according to manufacturer's guidelines. Cell blocks were either prepared using the Cellient method (Hologic, Marlborough Mass) or by the thrombin clot technique followed by formalin-fixation and paraffin-embedding. Immunohistochemical stains were performed on a subset of cases on the cell block sections. Clinical history and presentation for all patients were retrieved and reviewed. The clinical data was obtained from the institution's electronic medical record system (Epic Systems Corporation, Verona, Wis). For uncommon malignancies involving the pericardial cavity, such as squamous cell carcinoma, small cell carcinoma, melanoma, and sarcoma, slides were pulled and reviewed. A few cases of adenocarcinoma were reviewed.

Results

Clinical presentation

We retrieved a total of 1022 cases. Of those, 824 (80.6%) were diagnosed as "negative for malignant cells"; 158 (15.4%) were diagnosed "positive for malignancy"; 38 (3.7%) were "atypical cells present"; and 2 (0.1%) were "unsatisfactory." We only focused on the malignant cases. The details of the histologic diagnoses are summarized in Table 1. The male-female ratio (0.86:1) slightly favors women. For female patients, the most common primary site is lung adenocarcinoma, followed by breast adenocarcinoma. For male patients, the most common primary site is also lung adenocarcinoma, followed by esophageal adenocarcinoma. Patients of all age groups (range from 8 days old to 85 years) are affected with mean age of 56 years.

The prognosis for patients with malignant pericardial effusions is poor. As the vast majority of the patients with malignant pericardial effusions presented at an advanced stage and were severely ill, many of them were sent to hospice care when the acute symptoms were under control. A large number of these patients were "actively dying" according to the medical chart when discharged and were lost for follow-up. Of the 26 patients in which follow-up was available, 5 (19.2%) died within 1 week of presentation with malignant pericardial effusion; 7 (26.9%) died within 1 month; and only 4 (15.4%) survived after 2 years.

Four patients had a survival of more than 2 years. One patient is a 24-year-old man with lung adenocarcinoma who presented with widespread metastases to the mediastinum, bilateral neck, abdomen, and axillary lymph nodes, in addition to his malignant pericardial effusion. After a mutation for anaplastic lymphoma kinase (*ALK*) was detected, he was treated with crizotinib and had excellent response.[8] He is currently doing well 3 years after his initial diagnosis. A second patient is a 51-year-old man with an *ALK*-mutated lung adenocarcinoma with metastases to the bones,