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Infectious disease consultations and newly diagnosed cancer patients

A single-center retrospective observational study

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Abstract

Noninfectious diseases may be diagnosed during infectious disease (ID) consultations. Among non-IDs, cancer diagnosis is important; however, epidemiological data describing the relationship between ID consultations and newly diagnosed cancer patients are scarce. This study described the frequency and tendency of new cancer diagnoses in patients after ID consultation.

This retrospective study included adult inpatients who underwent ID consultations between October 2016 and March 2018. The demographic data and clinical manifestations of each case are described.

Among the 380 inpatients who underwent ID consultations, 6 (1.6%) received a new cancer diagnosis after ID consultation. Among the initial most likely diagnoses, 3 patients were diagnosed with IDs and 3 were diagnosed with non-IDs. The initial most likely ID diagnosis was important for new cancer diagnoses ($P = .004$, odds ratio: 11.1, 95% confidence interval: 2.11–57.2); diagnostic errors, as judged by the physicians, occurred in 2 of the 6 cases.

While the frequency of establishing new diagnoses during ID consultations is low, coexisting infection and cancer is possible. ID specialists should identify any patterns related to new cancer diagnosis in patients to prevent diagnostic error and improve the quality of diagnosis.

Abbreviations: CI = confidence interval, CT = computed tomography, FUO = fever of unknown origin, ICU = intensive care unit, ID = infectious disease, IQR = interquartile range, MRI = magnetic resonance imaging.

Keywords: cancer diagnosis, diagnostic error, infectious disease consultation

1. Introduction

Infectious disease (ID) specialists are important in medical care and ID consultations have gradually been recognized in Japanese hospitals.[1,2] Diagnostic consultations in cases of unexplained fever or symptoms are challenging for ID consultants. Although most ID consultation cases are IDs, the final established diagnoses are sometimes non-IDs such as drug fever, collagen vascular diseases, autoimmune diseases, and cancer.[3–5] Additionally, ID consultations with the purpose of treating patients may result in the diagnosis of new non-IDs. The early diagnosis of cancer, considered a non-ID, can improve patient prognosis. Therefore, it is important to learn the patterns associated with the diagnosis of cancer during ID consultations. However, epidemiological data on the relationship between ID consultations and newly diagnosed cancer patients are not available.

This study described the frequency and tendency of establishing new cancer diagnoses in patients after ID consultation. We further present information that can be used by ID specialists for diagnoses during ID consultations in tertiary acute-care teaching hospitals.

2. Material and Methods

2.1. Study design

This single-center retrospective observational study was conducted at St. Mary's Hospital (a 1097-bed acute tertiary care teaching hospital in Kurume, Japan) between October 2016 and March 2018. This hospital, which is located at a regional hub city in southwestern Japan, does not offer a diagnostic consultation service and does not have a diagnostic department such as the General Internal Medicine Department. This study was approved by the Research Ethics Committee of St. Mary's Hospital (No. 17-0203). ID consultations are part of the daily standard of patient care. The requirement for obtaining written consent from study participants was waived by the institutional review board because of the observational nature of the study without any deviation from current medical practices.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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2.2. Inclusion and exclusion criteria

We enrolled consecutive inpatients aged ≥18 years for whom an ID consultation was requested. We analyzed the ID consultation database; patients who underwent formal ID consultations were eligible for the analysis, while those who underwent informal (so-called "curbside") consultations, consultations not related to patient management such as infection control and surgical antimicrobial prophylaxis, were excluded. Moreover, patients who had already been diagnosed and eventually treated for cancer at the time of ID consultations were excluded; however, those who were successfully treated for cancer and who completed the regular follow-up were included. The following demographic data were collected: age, sex, requesting department, consultation location (general ward or intensive care unit [ICU]), initial clinical diagnosis of ID, causative organism, bacteremia status, presence or absence of ID diagnostic error, clues for cancer diagnosis, and final cancer diagnosis. The initial reasons for the ID consultation were categorized as diagnosis and management (fever or elevated levels of inflammatory markers including white blood cell count or C-reactive protein, fever of unknown origin [FUO], suspicion of infection, positive blood culture), and treatment of established infections (management of already-diagnosed infections such as intra-abdominal infection, respiratory infection, and urinary tract infection). Diagnostic error was defined as any mistake or failure in the diagnostic process leading to a misdiagnosis, missed diagnosis, or delayed diagnosis.[6]

2.3. Statistical analysis

Categorical variables were analyzed using either χ^2 or Fisher exact tests, while continuous variables were represented as medians with the interquartile range (IQR) and compared using Mann–Whitney *U* tests. Variables were compared between newly diagnosed cancer patients and non-cancer-diagnosed patients by univariate analysis with odds ratios and 95% confidence intervals. Statistical significance was defined as 2-sided *P* values $< .05$, and all statistical analyses were performed using JMP Pro (version 13.0, SAS Institute, Cary, NC).

3. Results

A total of 536 patients (≥18 years) underwent ID consultations during the study period. Based on the exclusion criteria, we excluded 26, 9, and 31 cases of infection control, surgical antimicrobial prophylaxis, and outpatient consultations. A total of 470 inpatients underwent ID consultations; of these, 90 had cancer. Finally, this study analyzed 380 patients.

Among the 380 inpatients who underwent ID consultations, 149 cases (39.2%) were requested by the Internal Medicine Department. The departments most frequently requesting consultations were surgery (n = 57, 15.0%), orthopedic surgery (n = 38, 10.0%), and cardiovascular surgery (n = 32, 8.1%) (Table 1). In the final diagnoses, 346 (91.1%) patients were diagnosed with IDs and 34 patients (8.9%) with non-IDs. Six patients (1.6%) were newly diagnosed with cancer after ID consultation. The clinical characteristics of the patients newly diagnosed with cancer are described in Table 2. The median patient age was 60 years (range, 42–81 years) (IQR, 45–79 years). The types of cancer included colon cancer (n = 3), uterine body cancer (n = 1), malignant lymphoma (n = 1), and acute myeloid leukemia (n = 1). The consultation settings included the general wards (n = 5) and ICU (n = 1). Among the initial most-likely diagnoses, 3 patients were diagnosed with ID (3/346, 0.9%) and 3 patients were diagnosed with non-ID (3/34, 8.8%). The incidence of the establishment of a new cancer diagnosis was higher in the non-ID group than that in the ID group and the initial most-likely ID diagnosis was important for new cancer diagnoses ($P = .004$, odds ratios: 11.1, 95% confidence interval: 2.11–57.2). The 2 cases of bacteremia were caused by *Streptococcus bovis* and *Pseudomonas aeruginosa*, respectively. Diagnostic errors, as judged by the reviewer's physicians, were observed in 2 of the 6 cases; thereafter, cancer was established as the final diagnosis (Table 2).

Table 1

Characteristics of the infectious disease consultations (n = 380).

Hospital departments	No. of patients
Surgery	57 (15.0%)
Orthopedic surgery	38 (10.0%)
Cardiovascular surgery	32 (8.4%)
Plastic surgery	29 (7.6%)
Emergency medicine	28 (7.4%)
Respiratory	28 (7.4%)
Nephrology	26 (6.8%)
Neurology	24 (6.3%)
Gastroenterology	20 (5.2%)
Dermatology	17 (4.5%)
Neurosurgery	16 (4.2%)
Cardiology	13 (3.4%)
Diabetes and endocrinology	12 (3.2%)
Rheumatology	11 (2.9%)
Psychiatry	10 (2.6%)
Gynecology	10 (2.6%)
Hematology	5 (1.3%)
Others	4 (1.1%)
Total	380 (100%)

Others: Ear, nose, and throat, urology.

4. Discussion

To our knowledge, this is the first epidemiologic study to describe the relationship between ID consultations and newly diagnosed cancer patients, including diagnostic error. In addition, this study is unique in terms of showing that the incidence of diagnosis through consultations by other medical specialties led to the diagnosis of neoplasm.

In this study, 6 patients (1.6%) were newly diagnosed with cancer after ID consultation, 3 of whom had colorectal cancer as the final diagnosis. In general, computed tomography (CT) is performed to evaluate, precisely examine, and detect fever; ID origin, and masses or nodules. The recent development of diagnostic imaging techniques has allowed easier recognition of masses, including solid mass. Therefore, the identification of large-sized solid masses during workup at the time of admission may be straightforward, including the identification of incidental cases such as obstructive pneumonia due to lung cancer and obstructive cholangitis caused by bile duct cancer. However, solid masses are difficult to detect in gastrointestinal cancer unless it has reached a certain size, such as in advanced cancer, especially in cases of ID consultations.

Diagnostic error is a relatively common outcome in any clinical setting and can lead to significant patient harm and healthcare costs. Diagnostic error is defined as delayed diagnosis, occurring

Table 2

Clinical profiles of the newly diagnosed after infectious diseases consultation.

Case no.	Age (yr)	Setting	Department	Underlying diseases	Reason for consultation	Chief complaints	ID initial clinical diagnosis	Causative microorganism	Diagnostic error	Clues for diagnosis	Final cancer diagnosis	Bacteremia	Outcome
1	40's	General ward	Nephrology	Chronic kidney disease	Treatment of abdominal abscess	Elevated CRP	Abdominal abscess	Unknown	Yes	Treatment failure → enhanced CT, colonoscopy	Rectal Cancer	Negative	Operation
2	50's	General ward	Surgery	Uterina myoma	Management of supprative arthritis	Fever buttock pain	FUO Left obtulor externus muscle pyomyositis with/without osteomyelitis	Unknown	Yes	Treatment Failure → Pubis biopsy	Uterine Body Cancer with bone metastasis	Negative	Palliative therapy
3	70's	General ward	Respiratory	None	Treatment of unsual organism of bacteremia	Fever, chills	*Streptococcus bovis* Bacteremia	*Streptococcus bovis*	No	Streptococcus bovis → colonoscopy	Rectal cancer	Positive	Operation
4	60's	General ward	Orthopedic surgery	Benign prostatic hyperplasia dementia	Management of Iliopsoas abscess	Left buttock pain	Left iliopsoas abscess	*Escherichia coli Klebsiella pneumoniae Bacteroides fragilis*	No	Unusuual causative pathogen operative history of rectal cancer 7 years ago (finish follow-up)	Rectal Cancer (reccurrence)	Negative	Operation
5	80's	General ward	Nephrology	Diabetes mellitus Focal glomerulosclerosis steroid user	FUO	Fever for 2 wk general fatigue	FUO splenomegaly spleen infarction	Unknown	No	Bone marrow aspiration Spleen biopsy	Intravasucular lymphoma	Negative	Chemotherapy
6	40's	ICU	Emergency medicine	Impaired glucose tolerance	Suspision of tick bite infection	Fever tick bite?	Cellulitis *Pseudomonas aerugonosa* bacteremia	*Pseudomonas aeruginosa* (blood culture) *Pseudomonas aeruginosa, MSSA, Eenterocuccs faecalis* (pus)	No	Blood smear bone marrow aspiration	Acute myeloid leukemia	Positive	Chemotherapy

FUO = fever of unknown origin, ICU = intensive care unit.

when the correct diagnosis is unintentionally delayed; wrong diagnosis, that is, another diagnosis was established before the correct diagnosis; and missed diagnosis, when a diagnosis was never established.[6] According to a previous analysis of 583 physician-reported diagnostic errors, lung cancer and colon cancer were the third (3.9%) and fourth (3.3%) leading causes of diagnostic error, respectively.[7]

The most common reasons for delays and errors in the diagnoses of cancers such as head and neck cancer were delays in being seen in the otolaryngology clinic after referral replacement, followed by diagnostic error by the referring physician.[8] To prevent diagnostic delays and errors, a literature review of diagnostic accuracy in anatomical pathology proposed the value of second opinions for diagnostic error prevention.[9] Another study reported the usefulness of a clinical decision support system for general practitioners.[10] Although the purpose of ID consultations is mainly to manage IDs, through a combination of second opinions, directed retrospective peer review, and participation in appropriate external quality assurance schemes, the risk associated with these diagnoses can be minimized with subsequent benefits to patient safety.

A retrospective case analysis of diagnostic error cases in Case 1 in this study indicated the presence of strong cognitive biases that might have led to diagnostic error (mainly delayed and wrong diagnoses), including availability bias (when things are the forefront of your mind because you have encountered the same cases before or have studied a disease that you have been focusing on), confirmation bias (the tendency to look for confirming evidence to support one's hypothesis and theory), and anchoring bias (anchoring the first piece of information and your idea when making decisions). In contrast, the main category of diagnostic error in Case 2 was incorrect and missed diagnosis. This case was affected by one of the strongest biases, "overconfidence bias," which usually occurs because of advice or ideas from respected supervisors and specialists in other fields or as a result of overconfidence in one's self in a clinical setting.[11] Furthermore, coinfection with cancer can be challenging because antibiotics may partially improve the condition.

Concerning nondiagnostic error cases in newly-diagnosed cancer patients in Case 3, a correlation between *Streptococcus bovis* biotype I (SBI) and *Clostridium septicum* and malignancies of the gastrointestinal tract has been widely reported.[12–15]*Streptococcus bovis*, a bacteremia-causing microorganism, may be a rare microorganism according to nonspecialists; however, among ID specialists, bacteremia due to SBI and *Clostridium septicum* are associated with colon malignancies. Although ID specialists are still scarce in Japan, it may be important for them to recommend colonoscopy to clinicians or microbiological laboratory in patients with these kinds of bacteremia.

In Case 4, the unusual pathogen of iliopsoas abscess was a diagnostic clue to rectal cancer. The main sources of secondary intestinal psoas abscess are the bone, gastrointestinal, and urinary tract.[16] A previous report indicated that approximately 20% of patients had diseases of gastrointestinal origin, while colorectal cancer occurred in 4.8% of patients with psoas abscess.[17]*Staphylococcus aureus* is the most common causative organism in patients with psoas abscess; gastrointestinal or genitourinary causes must be ruled out in cases of psoas abscess with uncommon causative organisms such as gram-negative rods or anaerobes.[17–19]

Regarding Cases 5 and 6, one of the major categories of FUO is malignant and neoplastic disorders. Malignant lymphoma is a common differential diagnosis as a cause of FUO.[20,21] In Case 5, FUO with splenomegaly was a clue to the establishment of diagnosis; the primary team consulted the ID specialists as other specialists had concluded that the possibility of lymphoma was low. After the diagnostic workup with no evidence of IDs, based on the results of the additional consultation, bone marrow aspiration was recommended. In Case 6, ecthyma gangrenosum (suspected to be a tick bite-like lesion) with pancytopenia was a diagnostic clue to acute myeloid leukemia.[22–25] This case was difficult to diagnose on the first day because there were no findings of leukemia such as blasts on the blood smear during admission. During the first ID consultation, the ID specialists observed that it would be unusual for this lesion to be due to tick bite; thus, the ID specialists ordered bone marrow aspiration to be performed. ID specialists should always keep the principle of "tissue is the issue" regardless of overconfidence bias, until proven otherwise.[26] Thus, we observed 3 types of newly diagnosed cancer patterns in this study; namely, diagnostic error (Cases 1 and 2), cases triggered by microorganisms (Cases 3 and 4), and categorized FUO cases (Cases 5 and 6).

This study has some limitations related to its retrospective and uncontrolled nature. We could not exclude diagnostic errors associated with the evaluation performed by the ID specialists. Second, since our results were based on ID consultations, there is a possibility that all cases could not be experienced. Third, this retrospective study was conducted at a single center in Japan; thus, the results may not apply to other settings, including other countries with different consultation styles such as university hospitals or hospitals with diagnostic departments including a General Internal Medicine Department. Finally, our results did not include informal consultations or ID consultations for outpatients. Nevertheless, our findings are valuable as they describe the relationship between ID consultations and newly diagnosed cancer patients in a tertiary-care teaching hospital. A future multicenter study with a large number of clinical cases is needed to elucidate the relationship between ID consultations and newly diagnosed cancer.

5. Conclusion

In conclusion, we described the frequency of the establishment of new cancer diagnoses in patients after ID consultations. It is important to keep in mind for all physicians, including ID specialists, that the frequency of establishing new cancer diagnosis is low (1.6% in this study); however, coexisting infection and cancer can occur, especially gastrointestinal cancer, in cases with nonenhanced CT. Further research is needed to describe the relationship between ID consultations and newly diagnosed cancer patients to improve the quality of ID consultations in daily practice, to prevent diagnostic error, and to improve patient prognosis.

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