Utility of an infectious and tropical disease histopathology diagnostic review service

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ABSTRACT

Aim To assess the utility of a London-based infectious and tropical disease histopathology diagnostic review service.

Methods The original and specialist review histopathology reports of 457 samples from over 3 years of referrals were compared retrospectively.

Results Overall 329 (72.0%) showed no significant difference; 34 (7.4%) showed a non-clinically significant difference; and 94 (20.6%) showed a clinically significant difference. Of the 94 clinically significant discrepancies, 46 (48.9%) were incorrectly suspected infections; 19 (20.2%) were missed infections; 8 (8.5%) were different infections; and in 20 (21.3%), the specialist review yielded more specific identification of an organism or a more correct assessment of its viability.

Conclusions A review of histopathology cases by an infectious disease (ID) histopathology referral centre has yielded a 20.6% clinically significant error rate. Measures to improve training in ID histopathology in the UK are discussed.

INTRODUCTION

The concept of error in medicine is well recognised, but diagnostic error in clinical medicine is difficult to define and measure because of the multiple and fluid parameters in play. In histopathology, the glass slides are archived and retained for a minimum of 10 years (according to Royal College of Pathologists UK guidelines), but often for much longer, allowing retrospective review. Review may either be by a peer (usually intradepartmental) or by a pathologist with a recognised greater degree of expertise in that field ('interdepartmental consultation').[1 2] Inevitably, a review by another pathologist will produce a difference of opinion in some cases, and then the question of the definition of 'diagnostic error' in histopathology arises.[3] Most studies divide these errors into those which have a clinical significance for patient management ('major disagreements/discrepancies') and those which do not ('minor disagreements/discrepancies'). These rates vary according to whether it is a 'general practice' or a 'specialist practice' which is being reviewed, with the former yielding an approximately 2%–3% clinically significant error rate.[1 4]

With the advent of globalisation and expansion of immunosuppressive and immunomodulatory therapies, infectious disease (ID) histopathology is a subspecialty that is growing in demand in resource-rich countries, despite a paradoxical, progressive loss of pathologists with expertise in the field.[5] Organ-based subspecialisation serves cancer diagnostics well, but not multisystem diseases, such as IDs. Moreover, because of the territorial overlap with microbiology/IDs and the prioritisation of cancer as a disease, ID histopathology is not a recognised subspecialty in the UK. Furthermore, the histopathology postgraduate curriculum no longer includes specific training in bacteriology, virology, mycology or parasitology. However, a missed or misdiagnosed ID, most of which are potentially curable and are common in patients under immunosuppression, many of them with cancer, often has serious consequences for the patient and sometimes the community, as regards morbidity, mortality and public health.

We present the first diagnostic review study of an ID histopathology service, that based at Guy's and St Thomas' NHS Foundation Trust (GSTFT) in London and serving the Hospital for Tropical Diseases (HTD) in London (part of University College London Hospitals NHS Foundation Trust).

MATERIALS AND METHODS

Aims

The aim of this retrospective service evaluation study was to assess the value of the ID histopathology diagnostic review service being undertaken on behalf of the HTD, and to highlight any trends in misdiagnosis/diagnostic discrepancy.

Case selection and retrieval

The histopathology computer records of all ID histopathology reviews performed at GSTFT on behalf of the HTD between 2015 and 2017, as well a proportion of cases from 2014 (selected consecutively from the electronic records), were retrieved. The remaining cases of 2014 were not analysed due to time constraints and because it was not anticipated that the overall trends and results would be affected by excluding them.

Where appropriate, cases consisting of multiple samples from a single patient were grouped and the overall original histopathology report diagnosis was compared with that of the specialist review diagnosis. Where these multiple samples were significantly different from each other (eg, from different organ systems), the diagnoses were compared for each sample individually. The following data were collected on each case:

GSTFT Histopathology accession number.
Patient's sex and age.
Originating histopathology laboratory.
Organ systems.

Table 1 Overall extent of agreement between the original and specialist histopathology reports

Year	Samples (n)	Non-significant difference	Non-clinically significant difference	Clinically significant difference
2017	153	107 (69.9%)	14 (9.2%)	32 (20.9%)
2016	136	98 (72.1%)	5 (3.7%)	33 (24.3%)
2015	94	71 (75.5%)	8 (8.5%)	15 (16.0%)
2014 (part)	74	53 (71.6%)	7 (9.5%)	14 (18.9%)
Total	457	329 (72.0%)	34 (7.4%)	94 (20.6%)

Original histopathology diagnosis.
Specialist review histopathology diagnosis.
Categorisation of differences between original and review diagnosis.

Comparison of original and specialist review histopathology reports

The extent of agreement between the original and the specialist histopathology reports was classified into one of three categories:

'No difference or non-significant difference', a very minor and possibly subjective difference in interpretation.
'Non-clinically significant difference', a discrepancy which would not have altered clinical management.
'Clinically significant difference', a discrepancy likely to have had implications for clinical management.

This assessment was performed by SYPY, and cases where categorisation was uncertain were reviewed by UM. Where there were multiple specimens which had been grouped as one sample, the most important diagnoses were chosen.

Further analysis of clinically significant discrepancies

The cases classified as 'clinically significant differences' were examined in greater detail, according to

1. Hospital of origin (London-based hospital, outside London UK hospital or hospital outside the UK).
2. Organ system (genitourinary, skin, lymphoreticular, gastrointestinal/salivary, respiratory, hepatobiliary, nervous system, postmortem or other, including cardiovascular, endocrine and material discharged from the body and suspected to be an organism).
3. Nature of discrepancy (incorrectly suspected infection, missed infection, different infection, more specific identification of organism or viability of organism and other, for example, neoplastic diagnostic discrepancy).

To identify if any particular ID was more likely to result in diagnostic discrepancy, discrepancies were also classified by major infections (schistosomiasis, *Candida*, *Histoplasma capsulatum*, leprosy, leishmaniasis, hydatid disease, *Entamoeba histolytica* and mycobacteria).

RESULTS

Number of cases and originating histopathology laboratories

The 331 cases studied consisted of all the cases available in 2017, 2016 and 2015, and 43 (out of the 101) cases from 2014. Eighteen cases were excluded due to the lack of an original histopathology report. A total of 313 cases met the inclusion criteria. As some of the cases consisted of multiple related samples, these 313 cases yielded 457 samples in total. The cases included in this study were received from 108 different hospitals/histopathology laboratories (26 London-based, 63 non-London UK-based and 19 outside the UK).

Overall discrepancies

Overall, 329 of 457 (72.0%) samples were classified as having no/non-significant differences between the original and the specialist histopathology reports; 34 of 457 (7.4%) samples were classified as having non-clinically significant differences; and 94 of 457 (20.6%) samples were classified as having clinically significant differences (table 1).

Clinically significant differences

Diagnosis

The samples with clinically significant discrepancies were further analysed to determine the nature of the discrepancy (table 2).

Overdiagnosis of an infection/organism, which on specialist review was judged not to be, was twice as common (48.9% of samples) as missing an infection (20.2% of samples). The infections most likely to be missed were schistosomiasis, mycobacterial infections (including tuberculosis and leprosy), leishmaniasis and amoebiasis. In the remaining 20% of the samples with clinically significant discrepancies, either a different or more specific infection was identified after specialist review, such as *Leishmania* spp being mistaken for *H. capsulatum*, or 'fungal infection' in the original report being refined to aspergillosis after specialist review, respectively; or there was an incorrect assessment of the viability of the organism, affecting clinical management, predominantly with schistosomiasis and hydatid disease. In the vast majority of cases, the specialist revision of the diagnosis was achieved by examining only H&E and other histochemical 'special' stains: it was the experience of the specialist reviewer, which rendered the diagnosis. In a few cases, the specialist ID referral centre had a wider repertoire of immunohistochemical stains than the referring laboratory, and this made the difference, for example, spirochaete, HIV P24 and toxoplasma. In even fewer cases (<1%), the refinement of diagnosis was achieved by molecular tests, which had generally been performed on duplicate fresh samples; for example, there was a case where the reporting histopathologist had recognised fungal hyphae, but PCR gave a specific identification of *Aspergillus delacroxii*.

Of the 67 clinically significant discrepancies which could be attributed to a specific infection (overcalling, undercalling, mistaken for another organism or incorrect viability assessment), helminth infections accounted for 49.2% (schistosomiasis 25.3%, hydatid disease 6.0% and other helminth 17.9%); mycobacteria for 16.5% (leprosy 7.5%, non-tuberculous mycobacteria 6.0% and tuberculosis 3.0%); leishmaniasis versus *H. capsulatum* for 6.0% and other leishmaniasis discrepancies for 7.5%; and other fungal discrepancies (apart from the distinction of *H. capsulatum* from *Leishmania*; these included

Table 2 Nature of clinically significant discrepancy between original report and specialist review

Nature of discrepancy	Samples (n) (total=94)
Incorrectly suspected infection	46 (48.9%)
Missed infection	19 (20.2%)
Different infection	8 (8.5%)
More specific identification of organism/viability	20 (21.3%)
Other (ie, neoplasia)	1 (1.0%)

Table 3 Clinically significant discrepancies attributable to a particular infection

Infectious disease entity	Samples (n) (total=67)
Schistosomiasis	17 (25.3%)
Hydatid disease	4 (6.0%)
Other helminth	12 (17.9%)
Leishmania versus *Histoplasma capsulatum*	4 (6.0%)
Other *Leishmania*	5 (7.5%)
Entamoeba histolytica	3 (4.5%)
Other protozoa	3 (4.5%)
Tuberculosis	2 (3.0%)
Leprosy	5 (7.5%)
Non-tuberculous mycobacteria	4 (6.0%)
Other bacteria	3 (4.5%)
Other fungi (apart from leishmaniasis vs *H. capsulatum*)	5 (7.5%)

H. capsulatum versus *Cryptococcus* and the misdiagnosis of *Candida*) for 7.5% (table 3).

For schistosomiasis-related discrepancies, approximately half were related specifically to the viability of the schistosome ova (figure 1), and the other half were related to whether or not ova were present. Viral infection clinically significant discrepancies were not encountered, probably because most histopathology departments have immunohistochemical/in situ hybridisation stains for the viruses commonly implicated in histopathology, for example, herpes simplex virus, cytomegalovirus, human herpes virus 8 and Epstein-Barr virus.

Organ system

The genitourinary system produced the highest proportion of clinically significant discrepancies (32.6%), reflecting the fact that the bladder is a common site for schistosomiasis, followed by respiratory (25.0%), hepatobiliary (24.5%), skin (22.6%) and gastrointestinal tract (16.9%) (table 4).

The four 'other' samples that resulted in clinically significant discrepancies consisted of samples of putative worms suspected to originate from the patient.

DISCUSSION

Diagnostic review in histopathology cases has been shown in several studies from different countries, to reveal an approximately 2%–3% clinically significant error rate,[1 4] but this rate is much greater when specialist centres have reviewed their referral cases: studies from UK sarcoma and liver pathology centres found 11% and 40% (respectively) major diagnostic discrepancies and 16% and 19% (respectively) minor discrepancies.[6 7]

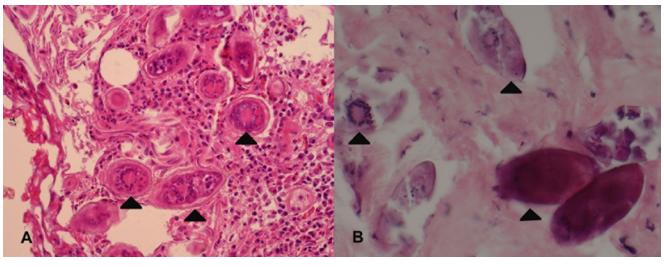

Figure 1 (A) Viable and (B) dead schistosome ova (arrowheads) (H&E).

This is the first study to evaluate an ID histopathology specialist review service and has shown that from a review of 457 samples referred to a UK ID histopathology centre, there was an approximately 20% rate of clinically significant discrepancies. This is unsurprising, given the low priority given to IDs in histopathology training, as compared with neoplasia, and their relative rarity in histology samples as compared with tumours. Unlike most of the other studies, our study has shown a lower rate of non-clinically significant discrepancies (approximately 7%), as compared with clinically significant ones (approximately 20%), emphasising that an incorrect diagnosis in ID pathology will often have an implication for patient management, because of the availability and specificity of antimicrobials. This also suggests that histopathologists are willing to issue reports on IDs when they are not entirely certain if they are correct. This may be because they perceive that microbiological investigations will provide a definitive answer, or because they feel that the chances of litigation are small, as compared with a misdiagnosis of neoplasia. However, the Association of Directors of Anatomic and Surgical Pathology in the USA has published guidelines for diagnostic review of histopathology cases, and the first listed reason for seeking an interdepartmental review is 'uncertainty of the referring pathologist about the diagnosis', which surely must hold whether the diagnosis relates to neoplasia or ID.[8]

On analysing the nature of the clinically significant discrepancies, we found that incorrectly suggesting an ID was more than twice as common as missing an infection (49% vs 20%). Because the reaction patterns provoked by infectious organisms are not specific, either to an organism or to IDs in general, a significant part of the job of an ID pathologist is offering an opinion as to whether the histopathological reaction pattern, such as granulomas, is due to an infection or something else, such as sarcoidosis or vasculitis; although this is based on the clinical context, experience and subtle morphological clues, if an organism is not found, this opinion at some point falls into a 'grey zone' of subjectivity. The possible infectious causes of granulomas are numerous, and the type of associated inflammatory cells/inflammatory pattern or location (suppurative, necrotising, eosinophilic and intraneural) may give a clue to the aetiological pathogen. Indeed, experience suggests that the difficult cases of tuberculosis represent one of the most challenging areas of ID histopathology.[9]

In 8.5%, review identified a different organism and in 21% was able to refine the identity of the organism or an opinion about its viability. This is clinically important because in modern ID clinical practice, the treatment is determined by the specific organism. The question of viability of organisms is clinically significant when it determines the necessity for treatment or the

Table 4 Organ systems of clinically significant discrepancies

Organ system	Samples with clinically significant discrepancies (n)/samples (total n) (%)
Gastrointestinal tract	25/148 (16.9%)
Skin	23/102 (22.6%)
Hepatobiliary	12/49 (24.5%)
Genitourinary	15/46 (32.6%)
Lymphoreticular	2/44 (4.6%)
Musculoskeletal	3/17 (17.7%)
Respiratory	4/16 (25.0%)
Postmortem material	1/2 (50.0%)
Other	4/7 (57.1%)

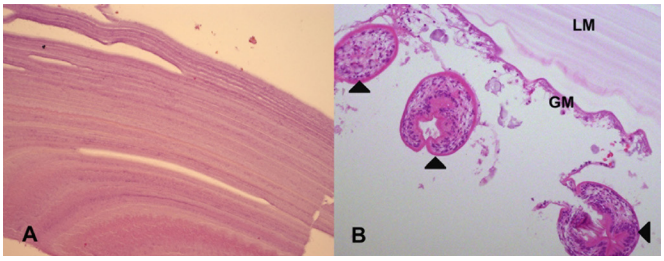

Figure 2 *Echinococcus granulosus:* (A) LM of a dead hydatid cyst and (B) LM with live GM and viable protoscoleces (arrowheads) (H&E). GM, germinal membrane; LM, laminated membrane.

duration of treatment, for example, with schistosome ova and hydatid cysts (figure 2).

Given the relative ease of international travel and the increased use of immunosuppression and immunomodulation, IDs are becoming more, rather than less, important. This is even disregarding the Pandora's box of HIV disease and opportunistic infections; although these are less common in the era of highly active antiretroviral therapies, immune reconstitution inflammatory syndrome reactions make their diagnosis even more challenging.[9 10]

This study has found an approximately 20% clinically significant discrepancy rate in a specialist ID histopathology diagnostic review service. We would recommend more prominent inclusion of IDs in the histopathology training curriculum, and for referral of cases to a specialist centre when there is diagnostic uncertainty. There are insufficient ID histopathology cases in the UK for every hospital to have a specialist, and a national review centre funded by the government/Public Health England (PHE) would be welcomed. The introduction of molecular diagnostic tests for micro-organisms, due to their sensitivity, has rendered the role of the histopathologist more, rather than less, important, as only the histopathologist can provide the morphological context of the organism found at a tissue level (contaminant vs commensal vs pathogen). The infectious organism molecular tests available for formalin-fixed paraffin wax-embedded (FFPE) material in the UK remain fairly limited to pan-bacterial (16 s), pan-fungal (18 s), fungal-specific and mycobacterial-specific assays. A national ID histopathology centre attached to PHE would also allow expansion of ID molecular diagnostic tests available for FFPE material, as well as maintenance of a repertoire of immunohistochemical stains for rare infections.[5 9]

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