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Critical review

Laboratory & Clinical Investigations

Clinical significance of p155 antibody in dermatomyositis

HL Gold[1*], GP Smith [2,3*]

Abstract

Introduction

Dermatomyositis is associated with an increased risk of malignancy, however, universal screening guidelines are not established. Recently the p155 antibody has been reported, along with an association with malignancy in dermatomyositis. The aim of this paper is to review the literature on the p155 antibody in DM and explore the implications this new marker may have in the clinical setting.

Materials and methods

We performed a Pubmed search, analysing all papers and those referenced within them for p155 antibody and dermatomyositis.

Results

A comprehensive review of the literature shows that p155 antibody is found at an increased incidence in dermatomyositis patients with underlying malignancy of any type, as well as in juvenile dermatomyositis and in those with more severe cutaneous involvement.

Conclusion

We conclude that p155 antibody may help clinicians diagnose juvenile dermatomyositis and identify those at risk for more severe disease. Although promising, further investigation is required to determine its role in cancer screening.

Introduction

Dermatomyositis (DM) is an idiopathic inflammatory condition of the skin and muscles. The link between DM and malignancy has been well established, with cancer being more common in DM than other types of inflammatory myopathies or other rheumatologic conditions[1].

Approximately 24% of cases are associated with an underlying malignancy. The majority of these malignancies are diagnosed within one year pre or post-dermatomyositis diagnosis[2], although the risk is elevated for at least three years. The most common neoplasms vary sharply by population, with studies in European and US populations most commonly identifying adeno-carcinoma of the ovary, lung, and gastrointestinal tract, whereas in Asian patients nasopharyngeal carcinoma is of more concern[2]. Given this association with malignancy, cancer screening is commonly pursued in patients with a diagnosis of dermatomyositis, however there is no consensus or clear guideline for how aggressively to work up a patient or how frequent screening should occur[3]. While some propose a simple review of systems and physical exam, with work-up only based on positive findings, others advocate annual screenings with radiologic exams and a full panel of serologic work-up including neoplastic markers.

Although this more aggressive screening approach may uncover more malignancy [4], it places patients at increased risk for iatrogenic harm by for example, radiation from repeated CT scans, adverse events from potentially unnecessary gastrointestinal scopes, or work-up for incidental, but clinically irrelevant, findings on such tests. A simple method to identify patients at increased risk would be instrumental in helping clinicians determine which patients would benefit from additional screening.

Recently, the p155 antibody was discovered as a novel serological marker shown to be associated with malignancy in DM patients. The target of this antibody has since been shown to be human transcriptional intermediary factor 1 γ (TIF1γ), a nuclear factor member of the TIF1 gene family[5]. While it is still early, at this stage studies have consistently shown an association between positive p155 antibody and malignancy detection in DM patients. Here we review the studies examining the p155 antibody in DM and the implications this new marker may have in the clinical setting.

Materials and Methods

Literature Search

In addition to the author's knowledge of the literature on this subject and their personal library of articles, a Pubmed search of "p155", "dermatomyositis and malignancy", and "dermatomyositis and autoantibodies" was performed, yielding 2355 articles.

After preliminary review for relevance, 23 articles remained. These articles were then reviewed for citations of other relevant articles and these were included in this review. In total 31 original articles contributed to this review.

Laboratory assays for p155 antibody detection

The majority of studies use immunoprecipitation (IP) to detect p155 antibodies, although ELISA and immunoblotting is also discussed. As background, the IP method (Figure 1) involves incubation of serum samples with Sepharose medium which binds any immunoglobulins present in the serum. Once bound, the medium is washed and exposed to Hela cell extract so that any immunoglobulins from the patient serum will bind their target protein. The serum antibody with target protein is then separated from the Sepharose, denatured, and run on an agarose gel to separate targeted proteins based on size. The studies then assess for the presence of a 155 kD protein. In contrast, for ELISA (Figure 2), a 96 well plate is coated with purified recombinant TIF1γprotein, the target protein of p155 antibodies.

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Serum samples are added to each plate, incubated, and then washed, leaving only antibodies that may have bound to TIF1γ. After washing, labelled anti-human IgG is incubated in each well and the presence of p155 antibody can be detected. A third approach for detection is the immunoblot (IB) for TIF1γ (Figure 3).

In this assay TIF1γ is run on a gel and transferred to nitrocellulose strips. Strips are then incubated with patient serum, washed, and then detected for presence of p155 antibody using labelled anti-human IgG antibody. The IB assay uses the same concept as ELISA but in place of a 96 well plate, one must prepare strips by running a gel of TIF1γand transferring it to nitrocellulose membrane. Of these tests ELISA is the easiest, least labour intensive, and unlike IP and IB, is offered in the common medical laboratory.

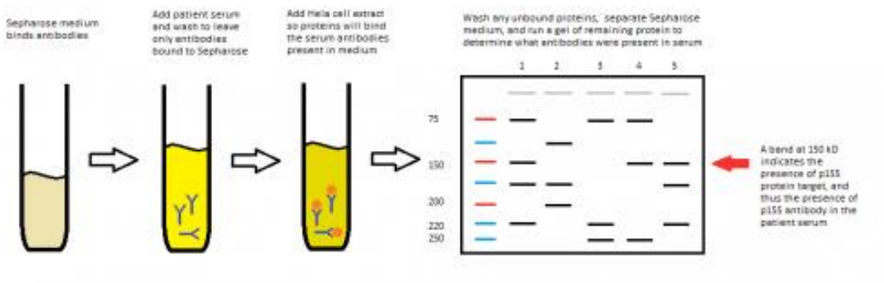

Figure 1: Immunoprecipitation method to detect p155 antibodies.

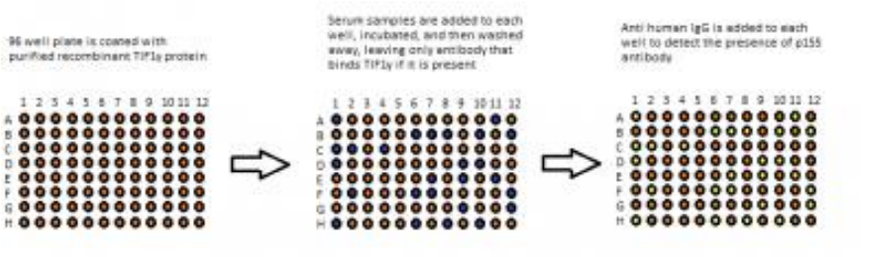

Figure 2: ELISA method to detect p155 antibodies.

Results

The anti-p155 antibody was reported as a novel autoantibody for dermatomyositis by Targoff et al.[6] in 2006. In that study sera from 244 myositis and 138 non-myositis patients was evaluated via immune-precipitation to identify unique autoantibodies in the idiopathic inflammatory myopathies (IIM). The p155 antibody was positive in 29% (30/103) of patients with juvenile dermatomyositis and 21% (8/39) of adult patients with DM. In contrast, it was not found in polymyositis patients (0/57).

Interestingly, they found it to be positive in 75% (6/8) patients with cancer associated myositis, and the overall rate of malignancy in the p155 antibody positive adult-DM group was 37.5% vs. 11.8% of the p155 antibody negative group. They also noted a lower incidence of interstitial lung disease in those with p155 antibody positive compared to the overall DM group (0% vs. 26%). Kaji et al.[7] performed a similar analysis assessing the sera of Japanese patients in a cohort of 52 patients with DM, 201 with other inflammatory diseases (9 polymyositis, 48 systemic lupus erythematosis (SLE), 126 systemic sclerosis (SS), 18 idiopathic interstitial pneumonitis (IIP)), and 50 healthy controls. They found 13% (7/52) patients with DM to be positive for p155 antibody. p155 antibody was not present in patients with non-myositis disease or in the healthy controls.

Overall, internal malignancy was found in 71% of patients with positive p155 antibody vs. 11% of those with negative p155 antibody. They also noted that heliotrope rash, Gottron's papules, and flagellate erythema was significantly associated with a positive p155 antibody. A study by Fujikawa[8] et al. looked at 30 DM patients and found that all patients positive for p155antibody (5/5) had cancer associated myositis (CAM). These studies concluded that the presence of p155 antibody was not only specific to DM, but also associated with malignancy and other clinical findings.

In a different approach, Chinoy et al.[9] sought to assess if p155 antibody could predict the risk of developing cancer in a cohort of 282 patients with IIM: 103 DM, 109 PM, and 70 myositis connective tissue overlap. 16 patients in the cohort developed CAM (15 DM patients and 1 myositis overlap). They again found p155 antibody to be positive exclusively in DM patients and associated with malignancy. p155 antibody was positive in 50% (8/16) of CAM patients vs. 4% (11/266) of patients in the non-CAM group. 7/8 patients with CAM and positive p155 antibody developed cancer within one year of diagnosis. In this patient population p155 antibody testing was 50% sensitive and 96% specific for CAM detection, with a 42% positive predictive value (PPV), and a high negative predictive value (NPV) as 97% of patients without p155 antibody did not have CAM. All patients were additionally screened for routinely detected antibodies (anti-Jo-1, anti-U1-RNP, anti-U3_RNP, anti-Ku, and anti-PM-Scl antibodies).

They found an association between CAM and a negative status for routine antibodies, and thus suggested combining p155 antibody status with routine antibody screening to increase the power of testing. Using both tests together, they reported 94% sensitivity and 99% NPV for CAM. Furthermore, when testing only the DM group they report that this method yields 100% sensitivity with a100% NPV.

Trallero-Araguás et al.[3] similarly evaluated p155 antibody as a serologic marker for cancer in a cohort of 85 myositis patients. Positive p155 antibody was found in 19% (16/85) of patients; 15 with DM and 1 with PM. In DM patients, p155 antibody was

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Table 1: Summary of findings of six original articles.

Authors	% DM with positive p155	% DM with p155 and CAM	% DM with p155 no CAM	% other IIM or other CTD with p155	% healthy with p155
Targoff et al.[5,6]	11% (14/37) adult DM 29% (30/103) juvenile DM	43% (6/14)	57% (8/14)	33% (5/15) juvenile CTD-associated myositis 0% (0/9) juvenile PM 2% (3/186) PM, CTD associated myositis, SLE, SSc, other CTD, other myopathy	0% (0/22)
Kaji et al.[7]	13% (7/52)	71% (5/7)	29% (2/7)	0% (0/201)	0% (0/50)
Fujikawa[8]	17% (5/30)	100% (5/5)	0% (0/5)	n/a	n/a
Chinoy et al.[9]	18% (19/103)	42% (8/19)	68% (11/19)	0% (0/179) PM and myositis/CTD overlap	n/a
Trallero-Araguás et al.[16]	23% (15/65)	67% (10/15)	33% (5/15)	5% (1/20) PM	n/a
Gunawardena et al.[19]	30% (6/20) adult DM 23% (27/116) juvenile DM	50% (3/6)	50% (3/6)	0% (0/215) PM, SLE, SSc	0% (0/50)

positive in 71.4% (10/14) with CAM vs. 9.8% (5/51) without CAM. They determined p155 antibody to have a 92% NPV and 66.7%PPV for CAM. p155 antibody positive DM patients were found to more commonly display shawl sign and V-sign (although not significant so), and have a lower incidence of ILD (0% vs. 42%).

In the original study of Targoff et al.[5,6], p155 antibody was reported as highly associated with juvenile dermato-myositis. This is interesting because in juvenile dermatomyositis most myositis markers are negative. Given this Gunawardena et al. [10] sought to evaluate the clinical significance of p155antibodies in juvenile DM. Overall they found 23% (27/116) of patients with juvenile DM to be positive for p155 antibody vs. 30% (6/20) of adults with DM. Additionally they found that those with positive p155 antibody had significantly more cutaneous involvement including a higher incidence of Gottron's papules, ulceration, and oedema. The distribution of skin lesions was also more extensive, most prominent over small and large joints and periorbitally.

In the adults tested, 50% (3/6) of those positive for p155antibody had malignancy while none who tested

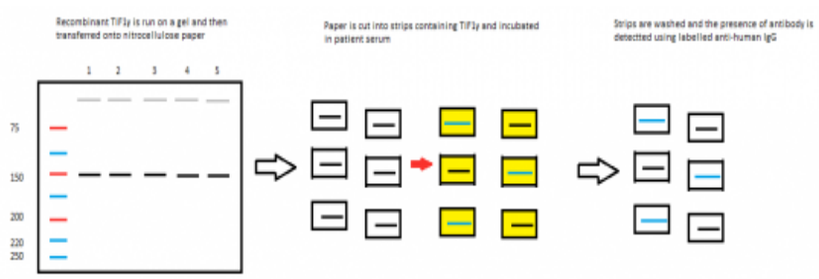

Figure 3: Immunoblot for detection of TIF1γ.

negative for p155 antibody had evidence of malignancy. They concluded that although malignancy does not generally occur in juvenile DM, p155 antibody is still clinically significant and may accurately predict those with a more severe and extensive disease course.

Two meta-analyses have been conducted pooling the results of the six studies mentioned above (summarized in table 1). Trallero-Araguás et al.[11] found a pooled sensitivity for CAM prediction to be 78% (95% CI 45–94%), with a specificity of 89% (95% CI 82–93). Using a pooled prevalence of 17% as pretest probability, they concluded that p155 antibody had a positive predictive value of 58% and a negative predictive value of 95%. Selva-O'Callaghan et al.[12] using these same 6 studies found an overall specificity of 89% (95% CI 85–93) and

Table 2: Autoantibodies in juvenile dermatomyositis.

Antibody	Frequency
Anti-P155	30-38.4%
Anti-MJ	20%
Anti-aminoacyl-tRNAsynthatases	3.1-5%
Anti-Mi-2	3.1-5%
Anti-SRP	0-2%

sensitivity of 70% (95% CI 56–82), with a negative predictive value of 93% and a diagnostic odds ratio of 18 (95% CI 8–40). This group also proposed a diagnostic algorithm incorporating the p155 antibody status, suggesting that a positive p155 antibody warranted yearly PET or CT scans for at least 3 to 5 years after diagnosis vs. just one PET or CT scan at DM diagnosis for those patients negative for p155 antibody. However, they highlighted the practical

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difficulty for implementation of p155 antibody screening in the clinical setting as all studies used immunoprecipitation for p155 antibody detection, a method unavailable to most medical centres.

Addressing the issue of practical implementation, Labrador et al.[13] investigated the feasibility of detecting p155 antibody using newly available ELISA assays for recombinant TIF1γ, the target molecule of p155. Their cohort consisted of 90 Spanish patients diagnosed with either amyopathic DM, CAM, or DM without cancer. They screened for p155 antibody using both classical immunoprecipitation (IP) and ELISA for TIF1γ and compared results. They found that anti-p155 IP and anti-TIF1γ ELISA results concurred in 96.7% (87/90) of patients, yielding a κ coefficient of 0.91. All patients with a positive ELISA were positive for both p155 antibody by IP and anti-TIF1γ by immunoblot. They concluded that the excellent concordance found was a promising step toward the general use p155 antibody screening in the clinical setting.

Discussion

Due to the proven association of cancer and DM, clinicians responsible for the management of these patients must make important decisions regarding not only how intensively to search for malignancy, but also how often to repeat these searches. As malignancy associated with DM most often occurs around the time of diagnosis of DM, it is imperative to provide rapid and timely evaluation.

This is an important issue for dermatologists, often the initial physicians to diagnose DM. Unfortunately, until now, stratification of patients according to risk of developing malignancy was mainly based on family history of malignancy, review of systems, and in some cases presence of specific cutaneous findings such as ulcerative skin lesions. While this approach will no doubt continue to yield important clinical value, it has low sensitivity to disease detection and misses many occult neoplasms.

The p155 antibody may present an opportunity to provide physicians with some guidance in providing cancer screening for their DM patients. The studies reviewed above show promising predictive power of this test. Meta-analyses of these studies allow for statistical analysis of over 300 patients with DM showing sensitivities approaching 70% and specificities approaching 90%. With a high specificity consistently reported, it is clear that once p155 antibody positive status is established, adult patients require close evaluation. What is still unclear is the screening to provide those patients with negative p155 antibody. Because of the seriousness of a cancer diagnosis, especially those associated with DM which hold a high mortality rate, a low sensitivity is not ideal for a screening test, and thus even in those with a negative p155 antibody cancer cannot be ruled out. For these reasons, this test should not be used in this manner. Additionally, it is known that autoantibodies may evolve and appear later in the disease course, thus it is not clear if and how often screening should be repeated following one negative result. We recommend a full history, physical, and routine age-appropriate screenings in all p155-negative patients, and at the least close clinical surveillance for malignancy in adult patients with positive p155 status.

It should be noted that to date evaluation of this marker has only been performed at a select few academic centres. A commercial test performed in everyday clinical situations rarely accurately reflects the sensitivity and specificity found under study conditions and this will also have to be re-evaluated once this testing becomes more commonplace. It should also be born in mind that the test has so far only been evaluated in a limited set of populations. Just as the specific type of cancer associated with DM varies with the population considered, it is likely that the sensitivity and specificity of this test will vary with population and the specific cancer present. While such evaluation will remain challenging in part due to the rarity of DM making large scale screenings difficult, over the course of time, with increased routine use of this test, its true clinical utility or lack thereof should become established.

Interesting is the possibility of combining p155 antibody with other commonly performed diagnostic tests to increase predictability. Chinoy et al.[9] state that by combining p155 antibody testing with other commonly performed antibody screens, one may achieve 100% sensitivity in CAM detection. However, this was only explored in one study involving 103 DM patients and only 16 patients with cancer. A larger study is warranted to confirm these findings. If confirmed this could lead to very accurate screening guidelines and would likely change the workup of DM patients.

Conclusion

p155 antibody in DM may end up being more clinically useful not for its association with malignancy, but instead for its other associations, and these should not be forgotten in any evaluation of the utility of this antibody. Several studies report an increase in the severity and extent of cutaneous symptoms with a positive p155 antibody and it therefore may serve as a marker in patients who will need more aggressive therapy early on or who should be followed at shorter intervals. As Gunawardena et al.[19] demonstrate, this is also positive more commonly in juvenile DM than any other marker and so may become the marker of choice in aiding the diagnosis in patients suspected of JDM (Table 2). Also reported was an inverse association with lung disease, as those with positive p155 consistently lacked lung involvement. A p155 negative status thus should prompt physicians to routinely monitor lung function in these patients. Taken together, the association of this antibody with several different phenotypic expressions of dermatomyositis may lead to a greater understanding of this 'idiopathic' disease. Hopefully, proper use of this screening assay will lead to

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better overall patient care and a reduction in the mortality and morbidity of dermatomyositis.

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