INFECTIOUS DISEASES

USING DOT-IMMUNOASSAY IN DECODING THE OUTBREAK OF PSEUDOTUBERCULOSIS IN THE TOMSK REGION

Zagoskina T.Yu.,
Markov E.Yu.,
Andreevskaya N.M.,
Klimov V.T.,
Nikolaev V.B.,
Dolgova T.M.,
Kolesnikova O.B.,
Gavrilova O.V.,
Kryukova A.V.,
Popova Yu.O.,
Starikova O.A.,
Doroshchenko A.A.,
Chesnokova M.V.,
Balakhonov S.V.

Irkutsk Antiplague Research Institute of Siberia and Far East of Rospotrebnadzor (Trilissera str. 78, Irkutsk 664047, Russian Federation)

Corresponding author:
Tatyana Yu. Zagoskina,
e-mail: t_y_z_@mail.ru

ABSTRACT

Background. *Pseudotuberculosis remains a serious healthcare problem, which determines the expediency of developing the express methods for its early diagnosis. To detect the pathogen, we designed test system for dot-immunoassay (DIA) based on antibodies labeled with silver nanoparticles (SNPs) isolated from hyperimmune rabbit serum obtained against killed cells of Yersinia pseudotuberculosis of O:1b serovariant.*

The aim. *To assess the possibility of using dot-immunoassay for express identification of Y. pseudotuberculosis cultures isolated from clinical material and environmental objects at the initial stage of bacteriological study during laboratory diagnosis of the disease.*

Methods. *We used the materials from the outbreak of pseudotuberculosis in the Krylovskaya Boarding School of the Bakcharsky district of the Tomsk region in 2021. Specific antibodies from hyperimmune rabbit sera obtained against Y. pseudotuberculosis 3704 particulate antigen of O:1b serotype were labeled with SNPs and used in DIA on nitrocellulose membranes with visualization of reaction results with a solution of a physical developer. The presence of the causative agent of pseudotuberculosis in the test material was inferred by the formation of gray spots of different intensity (from 4+ to 1+).*

Results. *All Y. pseudotuberculosis strains isolated using bacteriological method on the second day of the study from clinical material obtained from sick people and environmental objects were detected in DIA at concentrations ≥ 3.1×10^4 microbial cells per milliliter (m.c./ml).*

Conclusion. *The designed test system for dot-immunoassay using SNPs as a marker of specific antibodies for the detection of Y. pseudotuberculosis in cultures isolated from swabs from vegetables and clinical material from patients, including those with mixed infection, allows us to detect a specific corpuscular antigen with a high sensitivity (≥ 3.1×10^4 m.c./ml), providing express identification of isolated cultures at the initial stage of bacteriological study.*

Key words: *Yersinia pseudotuberculosis, pseudotuberculosis, specific hyperimmune serum, colloidal silver nanoparticles, dot immunoassay*

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ИСПОЛЬЗОВАНИЕ ДОТ-ИММУНОАНАЛИЗА ПРИ РАСШИФРОВКЕ ВСПЫШКИ ПСЕВДОТУБЕРКУЛЁЗА В ТОМСКОЙ ОБЛАСТИ

Загоскина Т.Ю.,
Марков Е.Ю.,
Андреевская Н.М.,
Климов В.Т.,
Николаев В.Б.,
Долгова Т.М.,
Колесникова О.Б.,
Гаврилова О.В.,
Крюкова А.В.,
Попова Ю.О.,
Старикова О.А.,
Дорощенко А.А.,
Чеснокова М.В.,
Балахонов С.В.

ФКУЗ Иркутский научно-исследовательский противочумный институт Сибири и Дальнего Востока Федеральной службы по надзору в сфере защиты прав потребителей и благополучия человека (664047, г. Иркутск, ул. Трилиссера, 78, Россия)

Автор, ответственный за переписку:
Загоскина Татьяна Юрьевна,
e-mail: t_y_z_@mail.ru

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РЕЗЮМЕ

Актуальность. *Псевдотуберкулёз остаётся серьёзной проблемой здравоохранения, что определяет целесообразность разработки экспрессных методов его ранней диагностики. Для обнаружения патогена нами сконструирована тест-система для дот-иммуноанализа (ДИА) на основе меченых наночастицами серебра (НЧС) антител, изолированных из гипериммунной кроличьей сыворотки, полученной против убитых клеток Yersinia pseudotuberculosis серовариантa O:1b.*

Цель исследования. *Оценка возможности использования дот-иммуноанализа для экспресс-идентификации культур Y. pseudotuberculosis, выделенных из клинического материала и объектов окружающей среды, на начальном этапе бактериологического исследования при проведении лабораторной диагностики заболевания.*

Методы. *В работе использованы материалы по вспышке псевдотуберкулёза в МКОУ «Крыловская школа-интернат» Бакчарского района Томской области в 2021 г. Специфические антитела из кроличьих гипериммунных сывороток, полученных против корпускулярного антигена Y. pseudotuberculosis 3704 серотипа O:1b, метили НЧС и использовали в ДИА на нитроцеллюлозных мембранах. О наличии в исследуемом материале возбудителя псевдотуберкулёза судили по формированию пятен серого цвета разной интенсивности (от 4+ до 1+).*

Результаты. *Все исследованные штаммы Y. pseudotuberculosis, выделенные бактериологическим методом из клинического материала от больных людей и объектов окружающей среды, обнаруживались в ДИА в концентрациях ≥ 3,1 × 10^4 микробных клеток в 1 мл (м.к./мл).*

Заключение. *Разработанная тест-система для ДИА с использованием НЧС в качестве маркера специфических антител для обнаружения Y. pseudotuberculosis в культурах, выделенных из смывов с овощей и клинического материала от больных, в том числе с микст-инфекцией, позволяет с высокой чувствительностью (≥ 3,1 × 10^4 м.к./мл) обнаруживать возбудитель псевдотуберкулёза, обеспечивая экспрессную идентификацию изолированных культур на начальном этапе бактериологического исследования.*

Ключевые слова: *Yersinia pseudotuberculosis, псевдотуберкулёз, специфическая гипериммунная сыворотка, наночастицы коллоидного серебра, дот-иммуноанализ*

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The economic damage caused by the 35 most pressing human diseases of infectious origin for the Russian Federation in 2015 amounted to 549 billion rubles [1]. Pseudotuberculosis is a natural focal saprozoonosis with a fecal–oral transmission [2], which is realized through infected food consumed raw or insufficiently heat-treated [3–6]. As a psychrophilic microorganism, pseudotuberculous microbe is able to proliferate at low temperature [7], form biofilm on refrigeration equipment and food products, accumulate on raw vegetables during their storage from autumn to winter [8], which causes a potential biological hazard to humans [9].

Enteropathogenic yersinia are the third most common etiological factor in the European Union after salmonellosis and campylobacteriosis causative agents [10]; pseudotuberculosis is registered almost everywhere in Russia in the form of sporadic and outbreak morbidity [11]. The occurrence of mass epidemic manifestations of this infection is also possible in natural and man-made emergency situations due to the occurrence of epizootics among rodents and, as a consequence, contamination of water and food by a causative agent in the areas of the affected population [12].

The effectiveness of anti-epidemic measures carried out in foci is determined by the timely detection of an etiological agent, the expressiveness and reliability of laboratory diagnostics. The most promising methods are those aimed at detecting the causative agent in biological material, food, water, swabs from environmental objects [13]. Dot-immunoassay (DIA) with antibodies labeled with silver nanoparticles (SNPs) is characterized by high sensitivity, compactability of analytical system (sample volume ~1–2 μl), ease of implementation and quick results (~1.5–2 hours), the possibility of non-instrumental use in field conditions. The test systems designed by us for DIA based on specific antibodies labeled with SNPs have been successfully tested for the detection of causative agents of plague, brucellosis, tularemia and botulinum toxin [14, 15].

THE AIM OF THE STUDY

To assess the possibility of using dot-immunoassay for express identification of *Y. pseudotuberculosis* cultures isolated from clinical material and environmental objects at the initial stage of bacteriological study during laboratory diagnosis of the disease.

MATERIALS AND METHODS

Experimental researches were conducted in accordance with the decision of the Council of the Eurasian Economic Commission No. 79 dated November 3, 2016 "On approval of the Rules of Good Clinical Practice of the Eurasian Economic Union", Order of the Ministry of Health of the Russian Federation No. 199n dated April 1, 2016 "On approval of the Rules of Good Laboratory Practice".

When working with animals, we were guided by: GOST 34088-2017 "Guidelines for the accommodation and care of laboratory animals. Rules for keeping and care of farm animals" (applicable from August 1, 2018); Directive 2010/63/EU of the European Parliament and of the Council of September 22, 2010 on the Protection of Animals used for Scientific Purposes; International Guiding Principles (Code of Ethics) for Biomedical Research Involving Animals (CIOMS, Geneva, 1985); European Convention for the Protection of Vertebrates Animals used for Experimental and other Scientific Purposes (Strasbourg, March 03, 1986).

We used materials on the etiological interpretation of the outbreak of pseudotuberculosis (from January 25 to February 2, 2021) at the Krylovskaya Secondary Boarding School for students with disabilities in the Bakcharsky district of the Tomsk region. 34 of affected people are reported to have the final diagnosis of "Pseudotuberculous infection". Two children had mixed infection of pseudotuberculosis + rotavirus infection; one child had mixed infection of pseudoturbeculosis + associated viral infection (rotavirus + norovirus infection). Secondary diagnosis: one child is a rotavirus carrier; 2 children are enterovirus carriers.

All patients were examined for causative agents of relevant intestinal infections by bacteriological method, polymerase chain reaction (PCR) (AmpliSens® OKI screen-FL, "AmpliSens *Yersinia enterocolitica/pseudotuberculosis*-FL", AmpliSens® Enterovirus-FL). The research was carried out by specialists of the laboratories of the Center for Hygiene and Epidemiology in the Tomsk Region and the bacteriological laboratory of the Tomsk Regional Clinical Hospital.

According to the results of the study, specific fragments of *Y. pseudotuberculosis* DNA were found in 7 samples by PCR. Rotavirus RNA was detected in two samples, norovirus RNA was detected in one sample and enterovirus RNA was detected in two samples. *Y. pseudotuberculosis* was isolated by bacteriological method in 6 cases from stool samples and in 1 case from urine sample.

27 samples of coprofiltrates from patients (material in a peptone-potassium medium) were sent to the Center for Surveillance of Yersinioses of Saint Petersburg Pasteur Institute of Epidemiology and Microbiology. Samples after "cold enrichment" were examined by PCR with AmpliSens® *Yersinia enterocolitica/pseudotuberculosis*-FL hybridization-fluorescence detection (Central Research Institute of Epidemiology, Moscow) with a set of reagents for detecting and differentiating DNA of virulent and avirulent strains of *Yersinia enterocolitica* and strains of *Yersinia pseudotuberculosis* in objects environment and clinical material. As a result, a culture of a pseudotuberculous microbe was isolated by bacteriological method in all samples where *Y. pseudotuberculosis* DNA was detected.

Specific hyperimmune serums were obtained by immunizing Chinchilla rabbits with *Y. pseudotuberculosis* inactivated strain No. 3704 of O:1 serotype [15]. Immunoglobulins G (IgG) isolated from the obtained sera [16] were labeled with SNPs of 5–9 nm size [17] and used in DIA,

which was carried out in a traditional way [14], involving the adsorption of the investigated material on the nitrocellulose membrane (NCM), blocking free areas of the solid phase with an inert protein solution. The detection of antigens adsorbed on NCM was carried out using labeled IgG, followed by visualization of the reaction results with a photodeveloper consisting of methol, citric acid and silver nitrate [18]. The presence of pseudotuberculosis causative agent in the studied material was judged by the formation of gray spots of different intensity (from 4+ to 1+) in the sample application sites, depending on the dilution of the studied material used.

RESULTS AND DISCUSSION

The work presents the results of a study of 8 *Y. pseudotuberculosis* cultures isolated from patients and 3 cultures isolated from swabs from vegetables during an epidemic outbreak in the Tomsk region, received by the Center for Indication and Laboratory Diagnostics of Irkutsk Antiplague Research Institute of Siberia and Far East for final identification. Considering that the bacteriological study is usually carried out for 15 (material from patients) and 21 days (material from environmental objects) with periodic seeding on the 2nd or 3rd, 5th, 7th, 10th or 15th and 21st days [19], we used dot-immunoassay as the method of express identification in the study of isolated cultures at the initial stage of bacteriological research. Culture seeding was performed in bromothymol blue medium (State Research Center for Applied Biotechnology and Microbiology, Obolensk) and incubated in a thermostat at +28 °C for 48 hours. At the stage of primary identification from the selected suspicious colonies (2–3 days), a suspension with a concentration of ~10^7 microbial cells in 1 ml (mc/ml) was prepared for analysis in DIA, inactivated by boiling in a water bath for 20 minutes, and after monitoring the specific sterility, each sample was titrated to determine the minimum concentration of the pathogen detected in dot-immunoassay, and each dilution of the material was applied to the membrane in a volume of 1 µl.

Detection of *Y. pseudotuberculosis* strains adsorbed on NCM in DIA (No. 1-11, No. 12 – *Y. pseudotuberculosis* 3704 O:1) was carried out at different concentrations. The analysis time did not exceed two hours. Samples containing pseudotuberculous microbe were detected on NCM in the form of gray spots with an intensity from 4+ to 1+ at concentrations of 12.5×10^4 – 3.1×10^4 mc/ml (Fig. 1).

The studied samples were determined in DIA in the following concentrations: strain No. 1 – 12.5×10^4 mc/ml; strain No. 2 – 12.5×10^4 mc/ml; strain No. 3 – 3.1×10^4 mc/ml; strain No. 4 – 3.1×10^4 mc/ml; strain No. 5 – 12.5×10^4 mc/ml; strain No. 6 – 6.2×10^4 mc/ml; strain No. 7 – 6.2×10^4 mc/ml; strain No. 8 – 3.1×10^4 mc/ml; strain No. 9 – 3.1×10^4 mc/ml; strain No. 10 – 6.2×10^4 mc/ml; strain No. 11 – 3.1×10^4 mc/ml. The control strain *Y. pseudotuberculosis* 3704 O:1 from the collection of the Department of Epidemiology, Irkutsk Antiplague Research Institute of Siberia and Far East, was detected at a concentration of 3.1×10^4 mc/ml. As negative controls, a sample of swab from a cabbage from a supermarket and a titration buffer were examined. All positive results obtained in dot-immunoassay were fully correlated with PCR and confirmed by further isolation of *Y. pseudotuberculosis* by a bacteriological method carried out according to the standard analysis scheme.

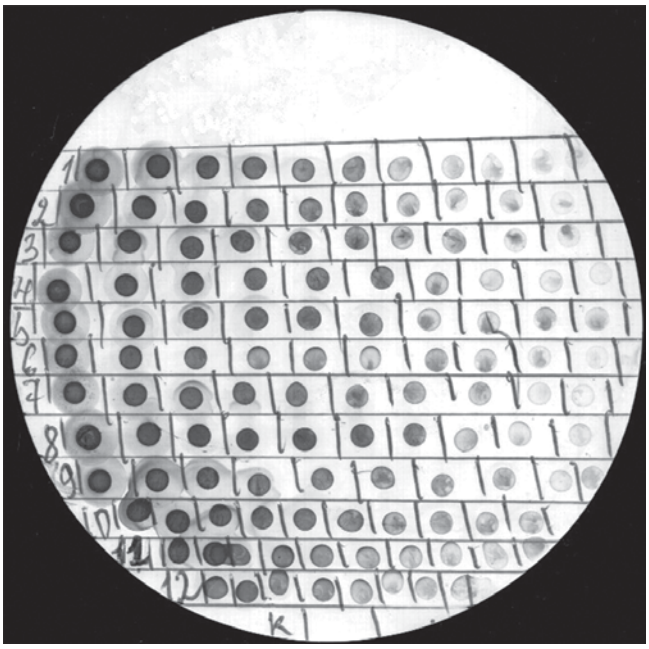

FIG. 1.
Detection of the causative agent of pseudotuberculosis in infectious material in dot-immunoassay: horizontal rows 1–8 – titrations of the studied corpuscular antigens from sick people; horizontal rows 9–11 – titrations of the studied corpuscular antigens from vegetables wipe samples; horizontal row 12 – Y. pseudotuberculosis 3704 O:1; "к" – negative controls

CONCLUSION

Thus, the reliably established possibility of using dot-immunoassay as an express method for determining *Y. pseudotuberculosis* in biological material and environmental objects at the stage of primary identification of selected suspicious colonies (2–3 days) during bacteriological analysis is of practical interest when conducting laboratory diagnostics of the disease in a shorter period of time and, consequently, accelerated verification diagnosis of pseudotuberculosis occurring with a variety of symptoms and syndromes, as well as during microbiological monitoring in order to control the effectiveness of anti-epidemic measures, including in the event of biological threats.

The results obtained indicate the high sensitivity of the developed test system for detecting the causative agent of pseudotuberculosis in DIA in the minimum volume of the studied sample (1 µl) for two hours.

The presented data demonstrate the high efficiency of DIA in express identification of the causative agent of pseudotuberculosis at the first stages of isolation of cultures from native material, which is confirmed by the results of a parallel study of the received samples in PCR and further isolation of *Y. pseudotuberculosis* by a bacteriological method carried out according to the standard analysis scheme.

Conflict of interest

The authors of this article declare the absence of a conflict of interest.

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Information about the authors

Tatyana Yu. Zagoskina – Dr. Sc. (Med.), Senior Research Officer, Head of the Department of Professional and Advanced Training, Irkutsk Antiplague Research Institute of Siberia and Far East of Rospotrebnadzor, e-mail: t_y_z_@mail.ru, https://orcid.org/0000-0002-9302-7143

Evgeny Yu. Markov – Dr. Sc. (Biol.), Head of the Department of Biochemistry, Irkutsk Antiplague Research Institute of Siberia and Far East of Rospotrebnadzor, e-mail: mark_evgenii@mail.ru, https://orcid.org/0000-0002-3693-7407

Nina M. Andreevskaya – Cand. Sc. (Biol.), Senior Research Officer at the Research and Production Department, Irkutsk Antiplague Research Institute of Siberia and Far East of Rospotrebnadzor, e-mail: adm@chumin.irkutsk.ru, https://orcid.org/0000-0002-8051-1809

Valery T. Klimov – Cand. Sc. (Med.), Senior Research Officer at the Department of Epidemiology, Irkutsk Antiplague Research Institute of Siberia and Far East of Rospotrebnadzor, e-mail: 41klimov@mail.ru, https://orcid.org/0000-0003-0036-0017

Valery B. Nikolaev – Cand. Sc. (Med.), Senior Research Officer at the Department of Biochemistry, Irkutsk Antiplague Research Institute of Siberia and Far East of Rospotrebnadzor, e-mail: balera58.58@mail.ru, https://orcid.org/0000-0001-7282-3696

Tatyana M. Dolgova – Research Officer at the Department of Professional and Advanced Training, Irkutsk Antiplague Research Institute of Siberia and Far East of Rospotrebnadzor, e-mail: adm@chumin.irkutsk.ru, https://orcid.org/0000-0003-1136-7468

Olga B. Kolesnikova – Cand. Sc. (Biol.), Senior Research Officer at the Department of Professional and Advanced Training, Irkutsk Irkutsk Antiplague Research Institute of Siberia and Far East of Rospotrebnadzor, e-mail: 89500884440@mail.ru, https://orcid.org/0000-0002-83-88-159x

Olga V. Gavrilova – Cand. Sc. (Biol.), Research Officer at the Department of Professional and Advanced Training, Irkutsk Antiplague Research Institute of Siberia and Far East of Rospotrebnadzor, e-mail: adm@chumin.irkutsk.ru, https://orcid.org/0000-0001-8349-2431

Anna V. Kryukova – Junior Research Officer at the Department of Biochemistry, Irkutsk Antiplague Research Institute of Siberia and Far East of Rospotrebnadzor, e-mail: anjakrukova@gmail.com, https://orcid.org/0000-0002-4850-0886

Yulia O. Popova – Laboratory Assistant at the Department of Biochemistry, Irkutsk Antiplague Research Institute of Siberia and Far East of Rospotrebnadzor, e-mail: adm@chumin.irkutsk.ru, https://orcid.org/0000-0003-4955-0751

Olga A. Starikova – Laboratory Assistant at the Department of Professional and Advanced Training, Irkutsk Antiplague Research Institute of Siberia and Far East of Rospotrebnadzor, e-mail: o.starickova@yandex.ru, https://orcid.org/0000-0003-3416-695X

Anton A. Doroshchenko – Junior Research Officer at the Department of Biochemistry, Irkutsk Antiplague Research Institute of Siberia and Far East of Rospotrebnadzor, e-mail: yashik.genry@mail.ru, https://orcid.org/0000-0002-5796-4260

Margarita V. Chesnokova – Dr. Sc. (Med.), Professor, Head of the Department of Scientific and Academic Support, Irkutsk Antiplague Research Institute of Siberia and Far East of Rospotrebnadzor, e-mail: mar_chumin@mail.ru, https://orcid.org/0000-0001-5489-9363

Sergey V. Balakhonov – Dr. Sc. (Med.), Professor, Director, Irkutsk Antiplague Research Institute of Siberia and Far East of Rospotrebnadzor, e-mail: adm@chumin.irkutsk.ru, https://orcid.org/0000-0003-4201-5828